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BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

RE: *U.S. Patent Application Entitled: COMPOSITIONS AND METHODS FOR EARLY PREGNANCY DIAGNOSIS - Robert Michael Roberts, Jonathan Andrew Green and Sancai Xie*

Sir:

Transmitted herewith for filing is a 94-page patent specification including 181 claims and an abstract. Also included is a 50 page sequence listing and Figures 1-6 on 6 sheets. The specification, drawings and sequence listing constitute the application of Robert Michael Roberts, Jonathan Andrew Green and Sancai Xie for the captioned invention.

Also transmitted herewith is a diskette containing the computer-readable form of those sequences in the specification, a Statement as Required Under 37 C.F.R. § 1.821(f), and a separate paper copy of the sequence listing.

Please note that this application is filed without an inventors Declaration and Assignment, a Declaration Claiming Small Entity Status, a Power of Attorney, and filing fees. Pursuant to 37 C.F.R. § 1.53(b) and (f), the Applicants request the Patent and Trademark Office to accept this application and accord a serial number and filing date as of the date this application is deposited with the U.S. Postal Service for Express Mail. Further, the Applicants request that the NOTICE OF MISSING PARTS-FILING DATE GRANTED pursuant to 37 C.F.R. § 1.53(f) be sent to the undersigned Applicants representative.

Please date stamp and return the enclosed postcard to evidence receipt of this application.

Please forward any reply to this communication directly to our Houston office for docketing purposes. The mailing address is P.O. Box 4433, Houston, Texas, 77210-4433; the physical address for courier packages is 750 Bering Drive, Houston, Texas, 77057, and the Houston fax number is 713.787.1440.

Respectfully submitted,

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Encl:

PATENT

UVMO:003

APPLICATION FOR UNITED STATES LETTERS PATENT

for

COMPOSITIONS AND METHODS FOR EARLY PREGNANCY DIAGNOSIS

by

ROBERT MICHAEL ROBERTS

JONATHAN ANDREW GREEN

and

SANCAI XIE

Express Mail No.: EL259185512US	
Date Of Deposit: March 19, 1999	

BACKGROUND OF THE INVENTION

This application claims priority to U.S. Provisional Application Serial No. 60/078,783 filed March 20, 1998 and U.S. Provisional Application Serial No. 60/106,188 filed October 28, 1998. The entire text of each of the above–referenced disclosures is specifically incorporated by reference herein without disclaimer. The government may own rights in the present invention pursuant to grant R37 HD29483 and USDA grant 9601842.

I. Field of the Invention

The present invention relates generally to the fields of veterinary medicine, reproductive biology and diagnostics. More specifically, the present invention relates to the use of analytical methods to detect early stage pregnancy.

II. Related Art

Pregnancy diagnosis is an important component in sound reproductive management, particularly in the dairy industry (Oltenacu *et al.*, 1990) where a high proportion of artificial inseminations fail (Streenan and Diskin, 1986). A reliable yet simple pregnancy test for cattle has long been sought. Several procedures are available, including a milk progesterone assay (Oltenacu *et al.*, 1990; Markusfeld *et al.*, 1990) estrone sulfate analysis (Holdsworth *et al.*, 1982; Warnick *et al.*, 1995), rectal palpation (Hatzidakis *et al.*, 1993), ultrasound (Beal *et al.*, 1992; Cameron and Malmo, 1993), and blood tests for pregnancy-specific antigens. Of these, the progesterone milk assay is the most cost effective for the producer (Oltenacu *et al.*, 1990; Markusfeld *et al.*, 1990). Next best is rectal palpation, performed at day 50 (Oltenacu *et al.*, 1990). Even though all the procedures are potentially useful, all have fallen short of expectations in terms of their practical, on-farm use. For example, measurements of milk or serum progesterone around day 18-22 yield unacceptably high rates of false positives (Oltenacu *et al.*, 1990; Markusfeld *et al.*, 1990). Rectal palpation can be used to detect pregnancy as early as

day 35, but this procedure can lead to 5-10% or greater embryonic mortality (Oltenacu *et al.*, 1990; Hatzidakis *et al.*, 1993). Rectal palpation on day 50 causes less damage to the embryos, but had only marginal economic value because of its lateness (Oltenacu *et al.*, 1990). Ultrasonography has an advantage over rectal palpation in accuracy, particularly before day 45 (Beal *et al.*, 1992; Cameron and Malmo, 1993), but the instrument is expensive, its use requires considerable training, and there is a finite risk to the animal. A related procedure, Doppler sonography, is more accurate than rectal palpation (Cameron and Malmo, 1993), but again requires well trained personnel. The presence of estrone sulfate in urine or serum provides another test but is only useful after day 100 as concentrations rise (Holdsworth *et al.*, 1982; Warnick *et al.*, 1995).

The discovery of pregnancy-specific protein B (PSP-B) (Butler *et al.*, 1982) provided a new approach to pregnancy diagnosis since it could be detected in the blood of pregnant cows by the fourth week of pregnancy (Sasser *et al.*, 1986; Humblot *et al.*, 1988). Two other groups have developed immunoassays that may be based on an identical or immunologically similar antigen (Zoli *et al.*, 1992a; Mialon *et al.*, 1993; Mialon *et al.*, 1994). In one case, the antigen (Mr ~67 kDa) was called bovine pregnancy-associated glycoprotein (boPAG; now boPAG-1) (Zoli *et al.*, 1992a); in the second, it was designated as pregnancy serum protein 60 (PSP60) (Mialon *et al.*, 1993; Mialon *et al.*, 1994). The immunoassay for PSP-B/boPAG1/PSP60 has two advantages. First, it can detect pregnancy relatively early. Second, interpretation of the assays does not require knowledge of the exact date of service, since boPAG-1 immunoreactive molecules are always present in the maternal serum of pregnant cows by day 28, and concentrations increase as pregnancy advances (Sasser *et al.*, 1986; Mialon *et al.*, 1993; Mialon *et al.*, 1994).

There remain, however, two major disadvantages to this procedure. First, positive diagnosis in the fourth week of pregnancy remains somewhat uncertain because antigen concentrations in blood are low and somewhat variable. Second, boPAG1 concentrations rise markedly at term (Sasser *et al.*, 1986; Zoli *et al.*, 1992a; Mialon *et al.*, 1993) and, due

to the long circulating half-life of the molecule (Kiracofe *et al.*, 1993), the antigen can still be detected 80-100 day postpartum (Zoli *et al.*, 1992a; Mialon *et al.*, 1993; Mialon *et al.*, 1994; Kiracofe *et al.*, 1993), compromising pregnancy diagnosis in cows bred within the early postpartum period. Thus, the test can be carried out in dairy cows at day 30 only if artificial insemination ("AI") is performed at or after 70 day post-partum.

A pregnancy test that could be carried out reliably and early in pregnancy could provide definitive indication as to whether rebreeding or culling is required. In general, AI is successful less than 50% of the time and the producer must either rely on overt signs of return to estrus (that are easily missed) or delay rebreeding until pregnancy failure is confirmed by one of the methods described above. Such delays are extremely costly and constitute a major economic loss to the industry. In the North Island of New Zealand alone, over two million cows are bred in a six-week period. A precise knowledge of the pregnancy status of these animals would be an invaluable aid to that and other diary industries worldwide. As should be apparent, this field has a need for a feasible, sensitive and accurate pregnancy test in cattle that can be performed by the end of the third week after insemination.

SUMMARY OF THE INVENTION

Therefore, it is an objective of the present invention to provide a sensitive and accurate test for early pregnancy. Using a selected boPAG as the biochemical marker, the present invention provides an early pregnancy test in which the PAG antigen a) is produced abundantly in early, and preferably not in late, pregnancy, b) is a product of the binucleate cell, and absent or not present in significant amounts postpartum, and c) minimally cross-reacts with late PAG products that might persist in maternal serum during the post-partum interval. The early immunoassay will be particularly useful in the dairy industry where animals are usually confined for at least part of the day and where intensive management is practiced. A modified test also is likely to have value in captive breeding programs for other animals, *e.g.,* for the ruminants okapi or giraffe and possibly for other non-ruminant species.

Thus, in a particularly preferred embodiment, there is provided a method for detecting pregnancy in a bovine animal comprising obtaining a sample from the animal; and detecting at least one of pregnancy associated antigen (PAG) wherein the PAG is present in early pregnancy and absent at about two months post-partum, whereby the presence of the PAG indicates that the animal is pregnant. Insemination is usually, but not invariably, performed about two months after calving in dairy cattle, until a successful conception results. The detection method may be applied within about 15 days of insemination and advantageously at about 20 to about 25 days after insemination. Given these facts, the time window for the disappearance of a useful PAG is about two months after calving, although earlier disappearance is also advantageous. However, PAGs which persist until about 65, about 70, about 75, about 80, about 85, about 90, about 95, or about 100 days after calving also are suitable for use. The exact day for this determination may vary depending on individual circumstances, however, given the teachings provided herein, an individual of skill in the art will understand the significance of testing for the absence of PAG during this time period and will be able to determine such a day. For example, if insemination occurs at a later date than 60 days post-partum, PAGs with a later disappearance profile may be useful. Thus, it is contemplated that the PAG of the present invention is detectable in early pregnancy but is not detectable at two months postpartum. Also, it is understood that the PAG indicative of early pregnancy may be absent in late pregnancy or present in amounts that are markedly less than those found in early pregnancy (for example, between day 15 and day 30 of pregnancy).

In particularly preferred embodiments, the PAG may be selected from the group consisting of PAG2, PAG4, PAG5, PAG6, PAG7 and PAG9. In more preferred embodiments, the PAG, independently, may be BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21.

In particular aspects of the present invention, the sample may be a saliva, serum, blood, milk or urine sample. Methods of sample collection are well known to those of skill in the art, for example, blood may be collected by needle from a tail vein or other blood vessel, milk withdrawn from the udder. Saliva and urine also may be collected according to well known techniques. In defined embodiments, it is contemplated that the detecting comprises an immunologic detection. In preferred embodiments, the immunologic detection comprises detection BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21 with polyclonal antisera. In alternative embodiments, the immunologic detection comprises detection of BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21 with a monoclonal antibody preparation. Immunologic detection methods are well known to those of skill in the art, in particularly preferred embodiment, the immunologic detection may comprise ELISA, in other embodiments, the immunologic detection may comprises RIA, in still further alternative embodiments, the immunologic detection comprises Western blot.

In certain aspects of the present invention, the method for detecting pregnancy may further comprise detecting a second PAG in the sample. The second PAG may be selected from the group consisting of BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21. Alternatively, the second PAG may be any other pregnancy associated glycoprotein used in the detection of pregnancy, for example, PAG1. Likewise the present invention contemplates a pregnancy detection method that further comprises detecting a third PAG in the sample.

In those embodiments employing ELISA as an immunological technique, it is contemplated that the ELISA may be a sandwich ELISA comprising binding of a PAG to a first antibody preparation fixed to a substrate and a second antibody preparation labeled with an enzyme. Sandwich ELISA is well known to those of skill in the art. In

particularly preferred embodiments, the enzyme may be alkaline phosphatase or horseradish peroxidase. In other embodiments, the first antibody preparation may be a monoclonal antibody preparation.

Other aspects of the present invention contemplate an antibody composition that reacts immunologically with BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21. Particularly preferred embodiments contemplate an antibody composition that reacts immunologically with BoPAG2. Other embodiments provide an antibody composition that reacts immunologically with BoPAG4. Further embodiments provide an antibody composition that reacts immunologically with BoPAG5. Still further embodiments contemplate an antibody composition that reacts immunologically with BoPAG6. Other embodiments contemplate an antibody composition that reacts immunologically with BoPAG7. Still further embodiments, contemplate an antibody composition that reacts immunologically with BoPAG9. It is contemplated that the antibody composition may be a monoclonal antibody composition or a polyclonal antibody composition.

The present invention further provides a hybridoma cell that secretes a monoclonal antibody that reacts immunologically with BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21.

Also contemplated herein is a method of making a monoclonal antibody to BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21 comprising the steps of immunizing an animal with a BoPAG preparation; obtaining antibody secreting cells from the immunized animal; immortalizing the antibody secreting cells; and identifying an immortalized cell that secretes antibodies that bind immunologically with the immunizing BoPAG.

Another aspect of the present invention provides a method of identifying a pregnancy associated glycoprotein (PAG) that is an early indicator of pregnancy in an Eutherian animal comprising the steps of obtaining a cDNA library prepared from the placenta of the animal between days 15 and 30 of pregnancy; and hybridizing the library under high stringency conditions with a PAG-derived nucleic acid probe; whereby hybridization of the probe identifies the PAG.

Also provided by the present invention is a method of identifying a pregnancy associated glycoprotein (PAG) that is an early indicator of pregnancy in an Eutherian animal comprising the steps of obtaining an RNA preparation from the placenta of the animal between days 15 and 30 of pregnancy; and performing RT- PCR™ on the preparation using PAG-derived primers; whereby amplification identifies the PAG.

In particularly preferred embodiments, the PAG detected in cattle (*Bos taurus*) may be any one or more of the following PAGs that are so far known to be produced in early pregnancy, namely: BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21. More specifically, the bovine PAGs that may be detected comprise the sequence of one or more of the following amino acid sequences: SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, and SEQ ID NO:32; SEQ ID NO:40; SEQ ID NO:42; SEQ ID NO:44; SEQ ID NO:46; SEQ ID NO:48; SEQ ID NO:50; SEQ ID NO:52; SEQ ID NO:54; SEQ ID NO:56. When applied to other species, the present invention will allow detection of other PAGs produced at the time the trophoblast (pre-placenta) begins either to attach or to implant into the uterine wall of the mother. The "early" PAGs in these species may cross-react immunologically with the PAGs useful in detecting early pregnancy in cattle.

The present invention contemplates an isolated and purified BoPAG2 polypeptide. In preferred embodiment, the BoPAG2 polypeptide comprises the sequence

of SEQ ID NO:25. Further, the invention contemplates an isolated and purified BoPAG4 polypeptide. In particularly preferred embodiments, the BoPAG4 polypeptide comprises the sequence of SEQ ID NO:27. Another embodiment contemplates an isolated and purified BoPAG5 polypeptide. A particularly preferred BoPAG5 polypeptide comprises the sequence of SEQ ID NO:28. Yet another embodiment provides an isolated and purified BoPAG6 polypeptide. In preferred embodiments, the BoPAG6 polypeptide comprises the sequence of SEQ ID NO:29. Another embodiment contemplates an isolated and purified BoPAG7 polypeptide. An especially preferred BoPAG7 polypeptide comprises the sequence of SEQ ID NO:30. Further contemplated by the present invention is an isolated and purified BoPAG9 polypeptide. In preferred embodiments, the BoPAG9 polypeptide comprises the sequence of SEQ ID NO:32. Further contemplated by the present invention is an isolated and purified BoPAG7v polypeptide. In preferred embodiments, the BoPAG7v polypeptide comprises the sequence of SEQ ID NO:40. Further contemplated by the present invention is an isolated and purified BoPAG9v polypeptide. In preferred embodiments, the BoPAG9v polypeptide comprises the sequence of SEQ ID NO:42. Further contemplated by the present invention is an isolated and purified BoPAG15 polypeptide. In preferred embodiments, the BoPAG15 polypeptide comprises the sequence of SEQ ID NO:44. Further contemplated by the present invention is an isolated and purified BoPAG16 polypeptide. In preferred embodiments, the BoPAG16 polypeptide comprises the sequence of SEQ ID NO:46. Further contemplated by the present invention is an isolated and purified BoPAG17 polypeptide. In preferred embodiments, the BoPAG17 polypeptide comprises the sequence of SEQ ID NO:48. Further contemplated by the present invention is an isolated and purified BoPAG18 polypeptide. In preferred embodiments, the BoPAG18 polypeptide comprises the sequence of SEQ ID NO:50. Further contemplated by the present invention is an isolated and purified BoPAG19 polypeptide. In preferred embodiments, the BoPAG19 polypeptide comprises the sequence of SEQ ID NO:52. Further contemplated by the present invention is an isolated and purified BoPAG20 polypeptide. In preferred embodiments, the BoPAG20 polypeptide comprises the sequence of SEQ ID NO:54. Further contemplated by the

present invention is an isolated and purified BoPAG21 polypeptide. In preferred embodiments, the BoPAG21 polypeptide comprises the sequence of SEQ ID NO:56.

Alternative embodiments of the present invention define an isolated and purified nucleic acid encoding BoPAG2. In particularly preferred embodiments, the BoPAG2 encoding nucleic acid comprises the sequence of SEQ ID NO:2. In other preferred embodiments, the BoPAG2 encoding nucleic acid encodes a BoPAG2 polypeptide comprising the sequence of SEQ ID NO:25.

Another embodiment provides an isolated and purified nucleic acid encoding BoPAG4. In preferred embodiments the BoPAG4 encoding nucleic acid comprises the sequence of SEQ ID NO:4. In other equally preferred embodiments, the BoPAG4 encoding nucleic acid encodes a BoPAG4 polypeptide comprising the sequence of SEQ ID NO:27.

In yet another embodiment, there is contemplated an isolated and purified nucleic acid encoding BoPAG5. In preferred embodiments, the BoPAG5 encoding nucleic acid comprises the sequence of SEQ ID NO:5. In other preferred embodiments, the BoPAG5 encoding nucleic acid encodes a BoPAG5 polypeptide comprising the sequence of SEQ ID NO:28.

In still another aspect of the present invention there is provided an isolated and purified nucleic acid encoding BoPAG6. In particularly preferred aspects the BoPAG6 encoding nucleic acid comprises the sequence of SEQ ID NO:6. In particularly preferred embodiments, the nucleic acid encodes a BoPAG6 polypeptide comprising the sequence of SEQ ID NO:29.

Also contemplated by the present invention is an isolated and purified nucleic acid encoding BoPAG7. In preferred embodiments, the nucleic acid comprises the

sequence of SEQ ID NO:7. In other preferred embodiments, the nucleic acid encodes a BoPAG7 polypeptide comprising the sequence of SEQ ID NO:30.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG9. In particular embodiments the BoPAG9 encoding nucleic acid comprises the sequence of SEQ ID NO:9. In other particularly preferred embodiments, the BoPAG9 encoding nucleic acid encodes a BoPAG9 polypeptide comprising the sequence of SEQ ID NO:32.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG7v. In particular embodiments the BoPAG7v encoding nucleic acid comprises the sequence of SEQ ID NO:39. In other particularly preferred embodiments, the BoPAG7v encoding nucleic acid encodes a BoPAG7v polypeptide comprising the sequence of SEQ ID NO:40.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG9v. In particular embodiments the BoPAG9v encoding nucleic acid comprises the sequence of SEQ ID NO:41. In other particularly preferred embodiments, the BoPAG7v encoding nucleic acid encodes a BoPAG9v polypeptide comprising the sequence of SEQ ID NO:42.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG15. In particular embodiments the BoPAG15 encoding nucleic acid comprises the sequence of SEQ ID NO:43. In other particularly preferred embodiments, the BoPAG7v encoding nucleic acid encodes a BoPAG15 polypeptide comprising the sequence of SEQ ID NO:44.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG16. In particular embodiments the BoPAG16 encoding nucleic acid comprises the sequence of SEQ ID NO:45. In other particularly preferred embodiments,

the BoPAG7v encoding nucleic acid encodes a BoPAG16 polypeptide comprising the sequence of SEQ ID NO:46.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG17. In particular embodiments the BoPAG17 encoding nucleic acid comprises the sequence of SEQ ID NO:47. In other particularly preferred embodiments, the BoPAG7v encoding nucleic acid encodes a BoPAG17 polypeptide comprising the sequence of SEQ ID NO:48.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG18. In particular embodiments the BoPAG18 encoding nucleic acid comprises the sequence of SEQ ID NO:49. In other particularly preferred embodiments, the BoPAG7v encoding nucleic acid encodes a BoPAG18 polypeptide comprising the sequence of SEQ ID NO:50.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG19. In particular embodiments the BoPAG19 encoding nucleic acid comprises the sequence of SEQ ID NO:51. In other particularly preferred embodiments, the BoPAG7v encoding nucleic acid encodes a BoPAG19 polypeptide comprising the sequence of SEQ ID NO:52.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG20. In particular embodiments the BoPAG20 encoding nucleic acid comprises the sequence of SEQ ID NO:53. In other particularly preferred embodiments, the BoPAG7v encoding nucleic acid encodes a BoPAG20 polypeptide comprising the sequence of SEQ ID NO:54.

Yet another embodiment contemplates an isolated and purified nucleic acid encoding BoPAG21. In particular embodiments the BoPAG21 encoding nucleic acid comprises the sequence of SEQ ID NO:55. In other particularly preferred embodiments,

the BoPAG7v encoding nucleic acid encodes a BoPAG21 polypeptide comprising the sequence of SEQ ID NO:56.

Also contemplated herein are oligonucleotides comprising at least 15 consecutive base pairs of any PAG encoding sequence, or a complement thereof, disclosed herein. Particularly contemplated is an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:9, or the complement thereof. In other embodiments, the oligonucleotide is about 20 bases in length. Also contemplated is an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:7, or the complement thereof. another embodiments contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:6, or the complement thereof. Yet another embodiments provides an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:5, or the complement thereof. In still a further embodiment, there is contemplated an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:4, or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:2 or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:39 or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:41 or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:43 or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:45 or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:47 or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:49 or the complement thereof. Yet another embodiment contemplates an

oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:51 or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:53 or the complement thereof. Yet another embodiment contemplates an oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:55 or the complement thereof. Of course it is understood that oligonucleotides of longer lengths are also contemplated including oligonucleotides of 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50 or more consecutive base pairs in length.

The present invention further provides a kit comprising a first monoclonal antibody preparation that binds immunologically to BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21; and a suitable container means therefor. It is contemplated that in particular embodiments, the kit may further comprise a second monoclonal antibody preparation that binds immunologically to the same BoPAG as the first monoclonal antibody, but wherein the first and the second monoclonal antibodies bind to different epitopes; and a suitable container means therefor. In particularly preferred aspects the first antibody preparation is attached to a support. It is contemplated that the support may be any support routinely used in immunological techniques. In particularly preferred embodiments, the support independently is a polystyrene plate, test tube or dipstick.

In particular embodiments, the second antibody preparation comprises a detectable label. The detectable label may be independently a fluorescent tag, a chemilluminescent tag, or an enzyme. In particularly defined embodiment, the enzyme is alkaline phosphatase or horseradish peroxidase. In further preferred embodiments, the kit may also comprise a substrate for the enzyme. In other embodiments, the kit may further comprise a buffer or diluent; and a suitable container means therefor.

In another embodiment, there is provided a kit including a first antibody composition that binds immunologically to BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21; and a suitable container means therefor as well as a second antibody composition that binds immunologically to the same boPAG as the first antibody composition, but the first and second antibody compositions bind to different epitopes; and included in this defined kit is a suitable container means therefor. More specifically, this aspect of the invention encompasses a second antibody composition including a detectable label. Other kit components, including reagent reservoirs, instructions and the like are well known to those of skill in the art and also are contemplated for use in the kits described herein.

In other embodiments, there is provided a method for detecting pregnancy in a non-bovine Eutherian animal comprising obtaining a sample from the animal; and detecting at least one of pregnancy associated antigen (PAG) in the sample, wherein the PAG is present in early pregnancy, whereby the presence of the PAG indicates that the animal is pregnant. The PAG may be absent at a period postpartum. As used herein, the term "absent" means not present using a given detection method. In other embodiments the PAG may be diminished postpartum. As used herein, "diminished" means dropping to undetectable or almost undetectable levels using a given protocol. In particularly preferred embodiment, the PAG may be selected from the group consisting of PAG2, PAG4, PAG5, PAG6, PAG7 and PAG9. In various embodiments, the animal in which pregnancy is being determined, may include all *Artiodactyla* which include *Suidae* (pigs and their relatives) and *Camellidae* (camels). It is contemplated that the animal may be a member of the suborder *Ruminantia*. In more defined embodiments, the Ruminantin may be a member of the family *Bovidae*. In more particular embodiments, the animal is a goat or sheep. In other embodiments the animal may be a member of the order *Perissodactyla*. In preferred embodiments, the animal may be a horse or rhinoceros. In alternative preferred embodiments, the animal is a member of the order *Carnivora*. More particularly the animal may be an animal of the canine or feline species. Even more

particularly, the animal may be a dog or a cat. In other embodiments, the animal may be a human or a panda.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1. Aligned amino acid sequences of different boPAGs. Each structure was inferred from the sequences of its cDNA. The likely signal sequence is underlined and a known site of propeptide sequence cleavage (ISG ↓RG/DS) for certain PAGs is shown (vertical arrow). Many additional sequences, some from cDNA not containing entire ORF, others differing less than 5% in nucleotide sequence from those shown, are known. Numbering at end of rows is by amino acid residue starting the Met1. Numbers in parentheses show the equivalent residue of pepsin. Boxes indicate the conserved sequences around the catalytic aspartic acid residues (Asp32 and Asp 215). GenBank Accession codes for boPAG1 through boPAG12 are M73961, L06 151, L06 153 and AF020506 through AF 020514, respectively.

FIG. 2. The aligned amino acid sequences of different ovPAGs. See legend to FIG. 1 for details. GenBank Accession codes for ovPAG1 through ovPAG9 are M73962, U30251 and U94789 through U94795, respectively.

FIG. 3. Summary of cloning data for boPAG expressed in day 19 and 25 bovine placenta. Early boPAG clones were identified by three independent procedures. Numbers indicate how many clones of identical sequence were isolated by each procedure. First, a day 25 bovine cDNA library was screened by homologous hybridization (Hybrid) with a probe consisting of ov, bo and poPAG1 and 2 as well as eqPAG cDNA. Sixteen clones with full length cDNA were purified and partially sequenced. The library was then immunoscreened (Immuno) with and anti-boPAG1 antiserum and 19 clones were purified and partially sequenced. RNA from a day 19 Holstein cow placenta was reverse transcribed and amplified with PCR™ (RT-PCR™). The PCR™ products were subcloned and partially sequenced. Note, most of the early boPAG were identified by homologous hybridization.

FIG. 4. Pairwise companions of the amino acid and nucleotide sequences of bovine PAG The data show percent nucleotide sequence identity (shaded) and percent amino acid sequence identity of translated sequences (unshaded).

FIG. 5. A phylogram based on amino acid sequences showing the relationship of all known cloned PAGs to common mammalian aspartic proteinases. The tree was constructed by the Wisconsin GCG programs Distances and GrowTree. The lengths of the branches are proportional to the degree of amino acid diversity within pairs of proteins. Protein data bank symbols: PEPA_pig, porcine pepsinogen A; PEPF_rabbit, rabbit pepsinogen F.

FIG. 6. Southern genomic blotting of DNA from some selected ruminant and nonruminant ungulate species and from a member of the family *Carnivora* (Panda). DNA was digested with *Eco*RI and probed with a boPAG1 probe. DNA size markers are

on the left. Some samples of DNA, *e.g.*, Suffolk Sheep and Mule Deer were analyzed twice.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

I. <u>The Present Invention</u>

Despite the availability of several assays to detect pregnancy, there remains a need to provide improved assays for accurate and early detection of pregnancy, especially in cattle that are bred within two to three months postpartum or earlier. In the context of the present invention, a preferred species is bovine. The present invention identifies several placentally expressed polypeptides, designated pregnancy associated glycoproteins (PAGs) that can be utilized to make early and accurate diagnoses of bovine and other pregnancies. Additional embodiments include the development of reagents from these polypeptides, and their corresponding genes, for use in assays to detect pregnancy. Extrapolation to other closely and distantly related species extends the application of these methods.

For use according to the present invention, selected PAGs are those that a) is produced abundantly in early and preferably not in late pregnancy, b) is a product of the binucleate cell, and absent or not present in significant amounts postpartum, and c) minimally cross-reacts with late PAG products that might persist in maternal serum during the post-partum interval. Further, the PAG should be detectable in serum at concentrations sufficient for a straightforward and rapid detection. Finally, the PAGs should be amenable to reproducible polyclonal and monoclonal antibody production in suitable host species. The remaining disclosure describes various features of the invention and their implementation.

II. <u>Pregnancy Associated Glycoproteins</u>

The placenta is the hallmark of the eutherian mammal. Rather than being the most anatomically conserved mammalian organ, however, it arguably is the most diverse (Haig, 1993). Placentation ranges from the invasive hemochorial type, as in the human,

where the trophoblast surface is in direct contact with maternal blood, to the epitheliochorial (*e.g.*, pig), where the uterine epithelium is not eroded (Amoroso, 1952). Not only is placental structure highly variable, the polypeptide hormones the placenta produces also vary between species (Haig, 1993; Roberts *et al.*, 1996). For example, no group of mammals other than higher primates possesses a chorionic gonadotrophin homologous to hCG for luteal support in early pregnancy, and only the ruminant ungulates are known to produce Type I interferon as an antilyteolytic hormone (Roberts *et al.*, 1996).

Placentation in ruminants, such as cattle and sheep, is superficial, relatively noninvasive, and known as synepitheliochorial cotyledonary (Wooding, 1992). 'Synepitheliochorial' describes the fetal-maternal syncytium formed by the fusion of trophoblast binucleate cells and uterine epithelial cells, whereas, 'cotyledonary' describes the gross structure of the placenta and specifically the tufts of villous trophoblast (cotyledons) that insinuate themselves into the crypts of the maternal caruncles. These regions of interdigitated and partially fused fetal cotyledonary and maternal caruncles are the placentomes and are the main sites for nutrient and gas exchange in the placenta. The binucleate cells, which compose about 20% of the surface epithelium (trophectoderm) migrate and fuse with maternal uterine epithelial cells and deliver their secretory products directly to the maternal system. Among the products are the placental lactogens (Wooding, 1981) and the pregnancy-associated glycoproteins (Zoli *et al.*, 1992a.)

Bovine pregnancy-associated glycoproteins (boPAGs), also known under a variety of other names including pregnancy-specific protein-B (Butler *et al.*, 1982), were discovered in attempts to develop pregnancy tests for livestock (Sasser *et al.*, 1986; Zoli *et al.*, 1991; Zoli *et al.*, 1992a). Rabbits were injected with extracts of placental cotyledons, and antibodies not directed against placental antigens were removed by adsorption with tissue extracts from nonpregnant animals. The resulting antisera provided the basis of an accurate pregnancy test for cattle and sheep as early as one month post-insemination.

Xie *et al.* (1991) used an antiserum directed against purified boPAGs from cattle and from sheep to screen cDNA libraries from late placental tissue. The full-length cDNAs shared 86% nucleotide sequence identities with each other and a surprising 60% sequence identity to pepsinogens. The boPAGs had mutations in and around their active sites that would render them inactive as proteinases (Xie *et al.*, 1991; Guruprasad *et al.*, 1996). The similarities to pepsin A (~50% amino acid identity) and chymosin (~45%) in primary structure has allowed atomic models of ovine (ov)PAG1 and boPAG1 to be built (Guruprasad *et al.*, 1996). Both molecules have the bilobed structure typical of all known eukaryotic aspartic proteinases and possess a cleft between the two lobes capable of accommodating peptides up to 7 amino acids long. Modeling strongly suggested that both ovPAG1 and boPAG1 can bind the pepsin inhibitor pepstatin, a prediction that has been validated.

Even in initial studies (Butler *et al.,* 1982*;* Zoli *et al.,* 1991*;* Xie *et al.,* 1991; Xie *et al.,* 1994; Xie *et al.,* 1996), it was clear that the boPAGs were heterogenous in molecular weight and charge, and as more isoforms have been purified it has become evident that they differ in their amino terminal sequences (Atkinson *et al.*, 1993; Xie *et al.*, 1997a). Further library screening has revealed additional transcripts in ruminants (Xie *et al.*, 1994; Xie *et al.*, 1995; Xie *et al.*, 1997b) and the existence of PAGs in non-ruminant species such as the pig (Szafranska *et al.*, 1995), and the horse (Guruprasad *et al.*, 1996).

Despite their apparent lack of proteolytic activity, all of the PAGs whose amino terminal sequences have been determined are proteolytically processed in a manner typical of other aspartic proteases such as pepsin (Davies, 1990). For example, a pro-peptide of most PAGs, which constitutes the first 38 amino acids of the secreted form and which normally folds into the active site region, has been cleaved from the secreted forms of PAG. Thus, the calculated molecular weight of the mature, non-glycosylated PAG, *i.e.* with signal sequence propeptide removed would be ~ 36,000 daltons and the circulating

antigen in serum would also lack this segment. The observed molecular weight of secreted PAG, however, is much larger ranging from 45,000 daltons to 90,000 daltons (Xie *et al.*, 1991; Sasser *et al.*, 1989; Xie *et al.*, 1996), probably due to extensive glycosylation (Holdsworth *et al.*, 1982). Multiple boPAG genes in the bovine genome have most likely contributed to the triphasic alterations of PAG concentrations in maternal serum.

A. BoPAG1

Bovine (bo) PAG1 was initially identified as a unique placental antigen by raising antisera to total bovine placental extracts (Zoli *et al.*, 1991). It is a product of binucleate trophoblast cells (Xie *et al.*, 1991; Zoli *et al.*, 1992b) which constitute the invasive component of the placenta (Wooding, 1992; Guillomot, 1995). In 1991, cDNA for both boPAG1 and ovine PAG1 was identified (ovPAG1) (Xie *et al.*, 1991). Surprisingly, the PAG1 belong to the aspartic proteinase (AP) gene family, a grouping that includes pepsin, chymosin, renin, and cathepsin D and E (Guruprasad *et al.*, 1996). Unlike other members of the AP family, both ovPAG1 and boPAG1 appear to be enzymatically inactive, since the catalytic domain in the active site region is mutated (Xie *et al.*, 1991; Guruprasad *et al.*, 1996).

BoPAG1 gene contains 9 exons and 8 introns (Xie *et al.*, 1996), an identical organization to that of other mammalian aspartic genes. Southern genomic blotting with a probe encompassing exon 7 and exon 8, which represent the most conserved region of PAG relative to other AP, indicated that there were probably many PAG genes. In addition, when a bovine genomic library was probed with boPAG1 cDNA, 0.06% positive phage plaques were identified, suggesting that there may be 100 or more PAG genes in the bovine genome (Xie *et al.*, 1995). This approximation has recently been confirmed by a variety of other approaches (Xie *et al.*, 1997b).

Levels of boPAG1 or related molecules that cross-react with a boPAG-1 antiserum are very low around day 21 to day 27 (Warnick *et al.*, 1995; Beal *et al.*, 1992;

Cameron and Malmo, 1993; Butler *et al.*, 1982), are maintained at a higher, but still low concentration until about day 100 of the pregnancy and then rise quickly to ~100 ng/ml. The concentrations then remain relatively constant until the last quarter of pregnancy when they peak at 1 μg/ml of serum or greater right before parturition. One explanation for the triphasic profile of boPAG1 immunoreactivity is that expression of boPAG1 is very low in early pregnancy, rises considerably at mid gestation and peaks before parturition (Sasser *et al.*, 1986; Zoli *et al.*, 1992a; Patel *et al.*, 1995). Alternatively, the presence of immunoreactive antigen in very early pregnancy may be due to the production of other boPAGs. The rise in the second trimester may reflect production of yet a different class of boPAG or possibly the initiation of low PAG1 expression. The exponential rise of boPAGs just prior to parturition could represent a sudden increase in the synthesis of one or more boPAG1 related molecules or increased "escape" across a leakier utero-placental junction.

Immunocytochemistry and *in situ* hybridization analyses have shown that boPAG1 and ovPAG1, and their close relatives (since neither the antisera nor the probes are expected to be monospecific) are localized to binucleate cells (Xie *et al.*, 1991; Zoli *et al.*, 1992b) In contrast, the antigenically distinct boPAG2 is expressed in predominantly mononucleate cells of the trophectoderm (Xie *et al.*, 1994). In the ruminants, binucleate cells are the invasive components of the trophoblast and do not appear until about day 13 in sheep and day 17 in cattle (Wooding, 1992). They then quickly increase in number. By day 21 in cattle they constitute up to 20% of cells in the trophectoderm, and a high percentage are actively fusing with maternal uterine epithelial cells (Wooding, 1992; King *et al.*, 1980; Guillomot, 1995). Binucleate cell granules, which contain PAG1 (Zoli *et al.*, 1992b), are discharged from the fusion cell towards the maternal stroma and its network of capillaries. Therefore, the binucleate cell products have ready access to the maternal circulation.

B. Novel OvPAG and BoPAG Species

According to the present invention, cDNA for a series of novel boPAGs have been identified and cloned (FIG. 1). A similar large family of ovine (ov) PAGs have been identified from sheep placenta (Xie *et al.*, 1991; Xie *et al.*, 1997a; Xie *et al.*, 1997b; FIG. 2). Certain of the boPAGs are useful in detection of early pregnancy in cattle. These molecules are homologous to, but different from, boPAG1 (Xie *et al.*, 1991; FIG. 1; FIG. 3). The inventors now estimate that there are at least 100 PAG-related genes in cattle, and the inventors have already cloned and wholly or partially sequenced at least 20 distinct cDNA (including 10 complete cDNA from early pregnancy). Apparently, PAGs constitute a polymorphic group (Xie *et al.*, 1994; Xie *et al.*, 1995; Xie *et al.*, 1997a; Xie *et al.*, 1997b), whose members either show variable degrees of immunocrossreactivity or do not cross-react at all with the antisera that have been developed. Some of the cloned PAGs are only expressed in binucleate cells of the placenta (see Example 3). These cells are known to have an endocrine function (Wooding, 1992). They produce placental lactogen and steroids, for example. However, the functions of the PAG family members are unknown, although they enter the maternal circulation.

One important aspect of the present invention is that PAGs are not expressed uniformly throughout pregnancy (see Example 4). Some are found early in pregnancy, while are others are expressed in later stages. For example, PAGs that are expressed most strongly in the invasive binucleate cells at implantation are not dominant in late pregnancy. Conversely, boPAG1 (PSP-B) (Xie *et al.*, 1991; Butler *et al.*, 1982; Sasser *et al.*, 1986) primarily is a product of binucleate cells of the late placenta, and antiserum raised against it fails to recognize the dominant PAG produced by binucleate cells in early pregnancy. Therefore, the test developed by the other groups and based on boPAG1/PSP-B/PSP60 (Butler *et al.*, 1982; Sasser *et al.*, 1986; Zoli *et al.*, 1992a; Mialon *et al.*, 1993; Kiracofe *et al.*, 1994) is only marginally useful early in pregnancy because the antigen is produced in extremely small amounts, if at all, at that time. The expression pattern of boPAG1 also helps explain the concentration profile of the antigen measured in

serum. At term, levels can exceed 5 μg/ml, while at day 40, when the development of the placenta in terms of size is almost complete, concentrations are around 10 ng/ml, *i.e.*, 500-fold lower.

Certain of the novel boPAGs disclosed in this invention (boPAG 4, 5, 6, 7, and 9), having the sequences of SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, and SEQ ID NO:32 are present at day 25 of pregnancy. These PAGs are expressed in invasive binucleate cells which release their secretory granules into maternal uterine capillary bed (see Example 3). Of these five, boPAG4 appears to cross react with the late pregnancy PAG, boPAG1, which has been the basis of the earlier pregnancy test (see Example 1). By virtue of their early expression, these PAGs can be detected by conventional immunological techniques in physiological fluids of heifers or cows (especially in serum, urine, and milk) to detect the presence of a fetus or fetuses in the uterus prior to day 30 of pregnancy. Thus, the presence of these antigens provide a diagnostic test of early pregnancy in cattle.

Similar observations on the diversity of PAGs, the localization of different PAGs to either mononucleated and binucleated cells, and the likely varied timing of PAG expression have been noted in sheep (Xie *et al.,* 1991; Xie *et al.,* 1997a; Xie *et al.,* 1997b). Because of the large number of genes noted in other species (FIG. 6) these observations are likely also to hold for other Artiodactyla, as well.

C. Structural, Functional and Evolutionary Aspects of PAGs

PAGs are members of the aspartic proteinase gene family (Xie *et al.*, 1991; Xie *et al.*, 1994; Xie *et al.*, 1995), although the inventors do not believe they are necessarily active as proteolytic enzymes. cDNAs for these antigens (called pregnancy-associated glycoproteins or PAG) have been cloned from early placenta and expressed in a variety of systems in order to produce recombinant products.

The active aspartic proteinases, which include the various pepsins, chymosins, cathepsin E and D and renin, are clustered in the central branches of the tree. Included among them is eqPAG1, which is paired with rabbit pepsinogen F. EqPAG1 is an active proteinase after propeptide excision (Green *et al.*, 1998) and may therefore be the horse homolog of pepsin F. Unfortunately little is known about pepsinogen F; it has been cloned from the stomach of a neonatal rabbit (Kageyama *et al.*, 1990), but its overall expression pattern in the fetus has not been studied, nor has pepsinogen F been described in any other species.

BoPAG1 and 2 occupy an intermediate position between the enzymatically functional aspartic proteinases and the PAGs from cattle and sheep. Of the latter, boPAG8, boPAG10 and ovPAG5 are the three most distant and possibly most ancient gene products so far identified. Most closely related to them are ovPAG2 and boPAG2, 11 and 12. As determined by *in situ* hybridization analysis, their genes are expressed in both the mononucleated as well as the larger invasive binucleated cells of the outer trophectoderm layer of the placenta. The remaining PAG genes, ovPAG1, 3, 4, 6, 7, 8 and 9 and boPAG1, 3, 4, 5, 6, 7 and 9, which have diverged less than the grouping above, have strictly binucleate cell-specific expression. Because binucleate cells are a typical feature of the trophectoderm of the synepitheliochorial placentas of the pecoran ruminants (suborder: Ruminantia) (Wooding, 1992), it is tempting to speculate that the PAG1 related genes diverged relatively recently.

If the entire PAG gene family arose by a series of relatively recent duplications during the diversification of the even toed ungulates (*Artiodactyla*), the expected lengths of the branches leading to the individual PAG might be expected to be relatively short. Instead many are long, far exceeding the distance between human, rabbit and rat cathepsin E (FIG. 8) whose divergence encompasses more than 100 million years of evolutionary time. There seem to be two alternative explanations. One is that the recent origin theory is wrong and that duplication of PAGs occurred early in the diversification of mammals. The second is that the genes duplicated late but accumulated mutations at a

high rate. Early diversification seems unlikely in view of the fact that large numbers of aspartic proteinase gene family members have not been described in either rodents or man despite considerable efforts to clone them (Birch and Loh, 1991). The inventors' data for the horse (*Perissodactyla*) and cat (*Carnivora*) indicate only a limited number (and possibly only a single) expressed PAG gene in each species. Therefore, the inventors favor a late and rapid diversification of the PAG within the Artiodactyla. In this regard, the relatedness of ovPAG2 and boPAG11 (94% at the amino acid level) suggests they are functional homologs. These genes are the most closely related of all the PAGs shown in FIG. 8, despite a species separation of around 18 million years (Miyamoto *et al.*, 1993).

An analysis (Nei, 1987; Li, 1993) of the nucleotide substitutions within the protein-coding regions of the PAG genes reveals that the ratio of synonymous (silent) mutations per synonymous site (Ks) to nonsynonymous (replacement) mutations per nonsynonymous site (Ka) in pairwise comparisons among all PAGs averages 1.18 ±0.27 (mean ± S.D.). A closer examination indicates that within highly conserved regions the Ks to Ka ratio is high, while it is low in the hypervariable loop-encoding regions. For example, the Ks to Ka ratio averages 3.07±1.08 for the highly conserved 29 codons encoding the buried carboxyl end of the molecules. By contrast, the value for the preceding 21 codons, which are hypervariable and encode the two loops (291-296 and 281-287) shown in FIG. 5B, is 0.53±0.18. Thus, mutations that alter amino acids have accumulated faster than silent mutations.

Mutations that lead to amino acid changes are much more likely to be deleterious and therefore to be eliminated than synonymous changes. For this reason Ks/Ka ratios are generally greater than 2.0 (Ohta, 1992). The PAGs appear exceptional in this respect, with the data suggesting that their high variability has occurred as the result of positive selection. Other related aspartic proteinases, such as ovine and bovine chymosins, enzymes whose coding regions are 95% identical in sequence (Moir *et al.*, 1982; Pungercar *et al.*, 1990) despite 18 million years of separation (Miyamoto *et al.*, 1993), exhibit a Ks to Ka ratio of 2.47, a value more than twice as high as the average PAG pair.

The only PAG pair that exhibits a comparable value to the chymosins is ovPAG2 and boPAG11 (ratio 2.92) proteins whose relatedness has been commented upon earlier (FIG. 8) and which may be functional homologs. Equine PAG and rabbit pepsinogen F, both active enzymes, provide a value of 2.61. Conceivably these genes have also acquired a function that is less able to tolerate changes in the surface loop regions than PAGs in general.

In a more general context, the evolution of multigene families has been the subject of several recent reviews (Ohta, 1995; Hughes, 1994; Fryxell, 1996). All agree that most duplicated genes are likely either to be quickly lost or accumulated as pseudogenes, as a result of "purifying" Darwinian selection, unless they acquire a novel function. By this argument it must be assumed that individual PAGs are not only functional molecules, but that each has a subtly different role. Hughes (1994) has argued that weak bifunctionality must be acquired prior to gene duplication and that, once duplicated, genes become separated by a burst of amino acid replacements that allows a specific function to become fixed and enhanced. These mutations are likely to be acquired by a combination of nonsynonymous point mutations, and by gene conversion events which can probably occur readily between closely linked, structurally similar genes (Ohta, 1995). Genetic drift and natural selection will ensure the retention of those mutations that are not deleterious. At present it is not possible to estimate what kinds of mutational changes contributed most to PAG diversity.

Fryxell (1996) has argued that the retention of a duplicated gene will in general, require the presence of a preexisting or similarly evolving family of complementary molecules with which the products of the duplicated genes can interact. Among the best known rapidly evolving gene families are immunoglobulins, T cell receptors and MHC antigens, the cytochrome p450 system and the odorant receptors. In each of these cases, diversification is linked to a more exacting capacity to bind particular ligands. For the PAGs, it is tempting to speculate that their function relates to their peptide-binding capabilities, although a function involving some structural feature other than the cleft,

such as the propeptide or carbohydrate, cannot be ruled out. Even though the regions around the two catalytic aspartyl residues are generally conserved in all aspartic proteinases (Davis, 1990; Takahashi *et al.*, 1995), substitutions elsewhere can markedly influence what peptides gain access to the catalytic center, clearly evident when the exceedingly narrow substrate specificity of renin is compared with that of pepsin A. The reorganization of the combining site of an antibody against a nitrophenyl phosphate hapten as it evolved from its germline precursor led to a 30,000-fold greater affinity for ligand and involved only a handful of amino acids, many of which were in a surface location and none of which made direct contact with the ligand (Wedemayer *et al.*, 1997). Small additive changes in the packing of loops provided a combining site able to lock in the hapten with much greater efficiency. Similar events could presumably modify the peptide-binding cleft of PAGs and provide molecules with a considerable range of specificities.

D. Variants of PAGS

It is contemplated that, for various uses, variants of PAGs can be utilized according to the present invention. These changes may improve stability or function, for example, antigenicity or immunoreactivity. It may be desirable to create substitutional, insertional or deletion variants or fusion proteins from the identified PAGs. Deletion variants lack one or more residues of the native protein. Insertional mutants typically involve the addition of material at a non-terminal point in the polypeptide. This may include the insertion of an immunoreactive epitope or simply a single residue. Terminal additions, are fusion proteins. Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein, and may be designed to modulate one or more properties of the polypeptide, such as stability against proteolytic cleavage, without the loss of other functions or properties. Substitutions of this kind may be termed "conservative," that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and include, for example, the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to

asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; and valine to isoleucine or leucine.

The following is a discussion based upon changing of the amino acids of a protein to create an equivalent, or even an improved, second-generation molecule. For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid substitutions can be made in a protein sequence, and its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the DNA sequences of genes without appreciable loss of their biological utility or activity, as discussed below. Table 1 shows the codons that encode particular amino acids.

Another embodiment for the preparation of polypeptides according to the invention is the use of peptide mimetics. Mimetics are peptide-containing molecules that mimic elements of protein secondary structure. See, for example, Johnson *et al.*, "Peptide Turn Mimetics" in *BIOTECHNOLOGY AND PHARMACY*, Pezzuto *et al.*, Eds., Chapman and Hall, New York (1993). The underlying rationale behind the use of peptide mimetics is that the peptide backbone of proteins exists chiefly to orient amino acid side chains in such a way as to facilitate molecular interactions, such as those of antibody and antigen. A peptide mimetic is expected to permit molecular interactions similar to the natural molecule. These principles may be used, in conjunction with the principles outline above, to engineer second generation molecules having many of the natural properties of PAGs, but with altered and even improved characteristics.

E. Purification of the Proteins

It will be desirable to purify the various PAGs identified by the inventors or variants thereof. Protein purification techniques are well known to those of skill in the art. These techniques involve, at one level, the crude fractionation of the cellular milieu to polypeptide and non-polypeptide fractions. Having separated the polypeptide from other proteins, the polypeptide of interest may be further purified using chromatographic and electrophoretic techniques to achieve partial or complete purification (or purification to homogeneity). Analytical methods particularly suited to the preparation of a pure peptide are ion-exchange chromatography, exclusion chromatography; polyacrylamide gel electrophoresis; isoelectric focusing. A particularly efficient method of purifying peptides is fast protein liquid chromatography or even HPLC.

Certain aspects of the present invention concern the purification, and in particular embodiments, the substantial purification, of an encoded protein or peptide. The term "purified protein or peptide" as used herein, is intended to refer to a composition, isolatable from other components, wherein the protein or peptide is purified to any degree relative to its naturally-obtainable state. A purified protein or peptide therefore also refers to a protein or peptide, free from the environment in which it may naturally occur.

Generally, "purified" will refer to a protein or peptide composition that has been subjected to fractionation to remove various other components, and which composition substantially retains its expressed biological activity. Where the term "substantially purified" is used, this designation will refer to a composition in which the protein or peptide forms the major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 90%, about 95% or more of the proteins in the composition.

Various methods for quantifying the degree of purification of the protein or peptide will be known to those of skill in the art in light of the present disclosure. These include, for example, determining the specific activity of an active fraction, or assessing

the amount of polypeptides within a fraction by SDS/PAGE analysis. A preferred method for assessing the purity of a fraction is to calculate the specific activity of the fraction, to compare it to the specific activity of the initial extract, and to thus calculate the degree of purity, herein assessed by a "-fold purification number" (*i.e.*, 2-fold, 5-fold, 10-fold, 50-fold, 100-fold, 1000-fold, *etc.*). The actual units used to represent the amount of activity will, of course, be dependent upon the particular assay technique chosen to follow the purification and whether or not the expressed protein or peptide exhibits a detectable activity.

Various techniques suitable for use in protein purification will be well known to those of skill in the art. These include, for example, precipitation with ammonium sulphate, PEG, antibodies and the like or by heat or acid pH denaturation of contaminating proteins, followed by centrifugation; chromatography steps such as ion exchange, gel filtration, reverse phase, hydroxylapatite and affinity chromatography; isoelectric focusing; gel electrophoresis; and combinations of such and other techniques. As is generally known in the art, it is believed that the order of conducting the various purification steps may be changed, or that certain steps may be omitted, and still result in a suitable method for the preparation of a substantially purified protein or peptide.

There is no general requirement that the protein or peptide always be provided in their most purified state. Indeed, it is contemplated that less substantially purified products will have utility in certain embodiments. Partial purification may be accomplished by using fewer purification steps in combination, or by utilizing different forms of the same general purification scheme. For example, it is appreciated that a cation-exchange column chromatography performed utilizing an HPLC apparatus will generally result in a greater "-fold" purification than the same technique utilizing a low pressure chromatography system. Methods exhibiting a lower degree of relative purification may have advantages in total recovery of protein product, or in maintaining the activity of an expressed protein.

It is known that the migration of a polypeptide can vary, sometimes significantly, with different conditions of SDS/PAGE and according to how extensively it is glycosylated (Capaldi *et al.,* 1977). It will therefore be appreciated that under differing electrophoresis conditions, the apparent molecular weights of purified or partially purified expression products may vary.

High Performance Liquid Chromatography (HPLC) is characterized by a very rapid separation with extraordinary resolution of peaks. This is achieved by the use of very fine particles and high pressure to maintain an adequate flow rate. Separation can be accomplished in a matter of min, or at most an hour. Moreover, only a very small volume of the sample is needed because the particles are so small and close-packed that the void volume is a very small fraction of the bed volume. Also, the concentration of the sample need not be very great because the bands are so narrow that there is very little dilution of the sample.

Gel chromatography, or molecular sieve chromatography, is a special type of partition chromatography that is based on molecular size. The theory behind gel chromatography is that the column, which is prepared with tiny particles of an inert substance that contain small pores, separates larger molecules from smaller molecules as they pass through or around the pores, depending on their size. As long as the material of which the particles are made does not adsorb the molecules, the sole factor determining rate of flow is the size. Hence, molecules are eluted from the column in decreasing size, so long as the shape is relatively constant. Gel chromatography is unsurpassed for separating molecules of different size because separation is independent of all other factors such as pH, ionic strength, temperature, *etc.* There also is virtually no adsorption, less zone spreading and the elution volume is related to molecular weight.

Affinity Chromatography is a chromatographic procedure that relies on the specific affinity between a substance to be isolated and a molecule that it can specifically bind to. This is a receptor-ligand type interaction. The column material is synthesized by

covalently coupling one of the binding partners to an insoluble matrix. The column material is then able to specifically adsorb the substance from the solution. Elution occurs by changing the conditions to those in which binding will not occur (alter pH, ionic strength, temperature, *etc.*).

A particular type of affinity chromatography useful in the purification of carbohydrate containing compounds is lectin affinity chromatography. Lectins are a class of substances that bind to a variety of polysaccharides and glycoproteins. Lectins are usually coupled to agarose by cyanogen bromide. Conconavalin A coupled to Sepharose was the first material of this sort to be used and has been widely used in the isolation of polysaccharides and glycoproteins other lectins that have been include lentil lectin, wheat germ agglutinin which has been useful in the purification of N-acetyl glucosaminyl residues and *Helix pomatia* lectin. Lectins themselves are purified using affinity chromatography with carbohydrate ligands. Lactose has been used to purify lectins from castor bean and peanuts; maltose has been useful in extracting lectins from lentils and jack bean; N-acetyl-D galactosamine is used for purifying lectins from soybean; N-acetyl glucosaminyl binds to lectins from wheat germ; D-galactosamine has been used in obtaining lectins from clams and L-fucose will bind to lectins from lotus.

The matrix should be a substance that itself does not adsorb molecules to any significant extent and that has a broad range of chemical, physical and thermal stability. The ligand should be coupled in such a way as to not affect its binding properties. The ligand should also provide relatively tight binding. And it should be possible to elute the substance without destroying the sample or the ligand. One of the most common forms of affinity chromatography is immunoaffinity chromatography. The generation of antibodies that would be suitable for use in accord with the present invention is discussed below.

F. Synthetic Peptides

The present invention also describes portions of PAG-related peptides for use in various embodiments of the present invention. Because of their relatively small size, the peptides of the invention can also be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. See, for example, Stewart and Young, (1984); Tam *et al.*, (1983); Merrifield, (1986); and Barany and Merrifield (1979), each incorporated herein by reference. Short peptide sequences, or libraries of overlapping peptides, usually from about 6 up to about 35 to 50 amino acids, which correspond to the selected regions described herein, can be readily synthesized and then screened in screening assays designed to identify reactive peptides. Alternatively, recombinant DNA technology may be employed wherein a nucleotide sequence which encodes a peptide of the invention is inserted into an expression vector, transformed or transfected into an appropriate host cell and cultivated under conditions suitable for expression.

G. Antigen Compositions

The present invention provides for the use of PAGs or peptides as antigens for the generation of polyclonal antisera and monoclonal antibodies for use in the detection of pregnancy. It is envisioned that some variant of a PAG, or portions thereof, will be coupled, bonded, bound, conjugated or chemically-linked to one or more agents *via* linkers, polylinkers or derivatized amino acids. This may be performed such that a bispecific or multivalent composition or vaccine is produced. It is further envisioned that the methods used in the preparation of these compositions will be familiar to those of skill in the art and should be suitable for administration to animals, *i.e.*, pharmaceutically acceptable. Preferred agents are the carriers such as keyhole limpet hemocyannin (KLH) or glutathione-S-transferase.

In order to formulate PAGs for immunization, one will generally desire to employ appropriate salts and buffers to render the polypeptides stable. Aqueous compositions of

the present invention comprise an effective amount of the PAG antigen to the host animal, dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium. Such compositions may be referred to as inocula. The phrase "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce adverse, allergic, or other untoward reactions when administered to an animal or a human. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well know in the art. Except insofar as any conventional media or agent is incompatible with the vectors or cells of the present invention, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

The compositions of the present invention may include classic pharmaceutical preparations. Administration of these compositions according to the present invention will be *via* any common route so long as the target tissue is available *via* that route. This includes oral, nasal, buccal, rectal, vaginal or topical. Alternatively, administration may be by orthotopic, intradermal, subcutaneous, intramuscular, intraperitoneal or intravenous injection. Such compositions would normally be administered as pharmaceutically acceptable compositions, described *supra*.

The PAGs also may be administered parenterally or intraperitoneally. Solutions of the active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile

injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial an antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the PAGs in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions of the present invention may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic,

tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, preparations should meet applicable sterility, pyrogenicity, general safety and purity standards.

III. <u>Nucleic Acids</u>

A. PAG-Encoding Sequences

The present invention provides, in another embodiment, genes encoding the various PAG polypeptides. Specifically, those encoding PAG2, PAG4, PAG5, PAG6, PAG7, and PAG9 are envisioned. Those nucleic acid sequences encoding the proteins having the sequences of SEQ ID NO:25; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:29; SEQ ID NO:30; and SEQ ID NO:32 are encompassed by the present invention, as are those polynucleotides disclosed in SEQ ID NO:2; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; and SEQ ID NO:9. The present invention is not limited in scope to these genes, however, as one of ordinary skill in the art could, using these nucleic acids, readily identify related PAGs in various other species.

In addition, it should be clear that the present invention is not limited to the specific nucleic acids disclosed herein. As discussed below, a given "PAG gene" may contain a variety of different bases and yet still produce a corresponding polypeptide that is functionally (*i.e.*, antigenically, immunologically), and in some cases structurally, indistinguishable from the genes disclosed herein.

Similarly, any reference to a nucleic acid should be read as encompassing a host cell containing that nucleic acid and, in some cases, capable of expressing the product of that nucleic acid. In addition to therapeutic considerations, cells expressing nucleic acids of the present invention may prove useful in the context of screening for agents that induce, repress, inhibit, augment, interfere with, block, abrogate, stimulate or enhance the detectability of PAGs.

Nucleic acids according to the present invention may encode an entire PAG gene, a domain of a PAG that contains a relevant epitope, or any other fragment of the PAG sequences set forth herein. The nucleic acid may be derived from genomic DNA, *i.e.*, cloned directly from the genome of a particular organism. In preferred embodiments, however, the nucleic acid would comprise complementary DNA (cDNA). At a minimum, these and other nucleic acids of the present invention may be used as molecular weight standards in, for example, gel electrophoresis.

The term "cDNA" is intended to refer to DNA prepared using messenger RNA (mRNA) as template. The advantage of using a cDNA, as opposed to genomic DNA or DNA polymerized from a genomic, non- or partially-processed RNA template, is that the cDNA primarily contains coding sequences of the corresponding protein. There may be times when the full or partial genomic sequence is preferred. It also is contemplated that a given PAG from a given species may be represented by natural variants that have slightly different nucleic acid sequences but, nonetheless, encode the same protein (see Table 1).

As used in this application, the term "a nucleic acid encoding a PAG" refers to a nucleic acid molecule that has been isolated free of total cellular nucleic acid. In preferred embodiments, the invention concerns a nucleic acid sequence essentially as set forth in for example, SEQ ID NO:25; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:29; SEQ ID NO:30; or SEQ ID NO:32. The term "as set forth in, for example, SEQ ID NO:25; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:29; SEQ ID NO:30; or SEQ ID NO:32 " means that the nucleic acid sequence substantially corresponds to a portion of SEQ ID NO:25; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:29; SEQ ID NO:30; or SEQ ID NO:32 respectively. The term "functionally equivalent codon" is used herein to refer to codons that encode the same amino acid, such as the six codons for arginine or serine (Table 1), and also refers to codons that encode biologically equivalent amino acids, as discussed in the following pages.

TABLE 1

Amino Acids			**Codons**					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

Allowing for the degeneracy of the genetic code, sequences that have at least about 50%, usually at least about 60%, more usually about 70%, most usually about 80%, preferably at least about 90% and most preferably about 95% of nucleotides that are identical to the nucleotides of FIG. 1 will be sequences that are "as set forth in FIG. 1." Sequences that are essentially the same as those set forth in FIG. 1 may also be functionally defined as sequences that are capable of hybridizing to a nucleic acid segment containing the complement of FIG. 1 under standard conditions.

Naturally, the present invention also encompasses DNA segments that are complementary, or essentially complementary, to the sequence set forth in FIG. 1. Nucleic acid sequences that are "complementary" are those that are capable of base-pairing according to the standard Watson-Crick complementary rules. As used herein, the term "complementary sequences" means nucleic acid sequences that are substantially complementary, as may be assessed by the same nucleotide comparison set forth above, or as defined as being capable of hybridizing to the nucleic acid segment of SEQ ID NO:2; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; or SEQ ID NO:9 under relatively stringent conditions such as those described herein. Such sequences may encode the entire PAGs encompassed herein or functional or non-functional fragments thereof.

B. PAG-Encoding Fragments

Alternatively, the hybridizing segments may be shorter oligonucleotides. Sequences of 17 bases long should occur only once in the human genome and, therefore, suffice to specify a unique target sequence. Although shorter oligomers are easier to make and increase *in vivo* accessibility, numerous other factors are involved in determining the specificity of hybridization. Both binding affinity and sequence specificity of an oligonucleotide to its complementary target increases with increasing length. It is contemplated that exemplary oligonucleotides of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more base pairs will be used, although others are contemplated. Longer polynucleotides are contemplated as well.

Such oligonucleotides will find use, for example, as probes in Southern and Northern blots and as primers in amplification reactions. These reagents are particularly useful in identifying structurally related PAGs.

Suitable hybridization conditions will be well known to those of skill in the art. In certain applications, for example, substitution of amino acids by site-directed mutagenesis, it is appreciated that lower stringency conditions are required. Under these conditions, hybridization may occur even though the sequences of probe and target strand are not perfectly complementary, but are mismatched at one or more positions. Conditions may be rendered less stringent by increasing salt concentration and decreasing temperature. For example, a medium stringency condition could be provided by about 0.1 to 0.25 M NaCl at temperatures of about 37°C to about 55°C, while a low stringency condition could be provided by about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

In other embodiments, hybridization may be achieved under conditions of, for example, 50 mM Tris-HCl (pH 8.3), 75 mM KCl, 3 mM $MgCl_2$, 10 mM dithiothreitol, at temperatures between approximately 20°C to about 37°C. Other hybridization conditions utilized could include approximately 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 µM $MgCl_2$, at temperatures ranging from approximately 40°C to about 72°C. Formamide and SDS also may be used to alter the hybridization conditions.

As stated above, one method of using probes and primers of the present invention is in the search for genes related to the PAG encompassed in the instant invention or, more particularly, homologs of PAG from other species. The existence of a variety of homologies strongly suggests that other homologs will be discovered in additional species. Normally, the target DNA will be a genomic or cDNA library, although screening may

involve analysis of RNA molecules. By varying the stringency of hybridization, and the region of the probe, different degrees of homology may be discovered.

Another way of exploiting probes and primers of the present invention is in site-directed, or site-specific mutagenesis. Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent proteins or peptides, through specific mutagenesis of the underlying DNA. The technique further provides a ready ability to prepare and test sequence variants, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Typically, a primer of about 17 to 25 nucleotides in length is preferred, with about 5 to 10 residues on both sides of the junction of the sequence being altered.

C. *Vectors for Cloning, Gene Transfer and Expression*

Within certain embodiments, expression vectors may be utilized to produce PAGs which can then be purified and, for example, be used to generate antisera or monoclonal antibody with which further studies may be conducted. Expression requires that appropriate signals be provided in the vectors, and which include various regulatory elements, such as enhancers/promoters from both viral and mammalian sources that drive expression of the genes of interest in host cells. Elements designed to optimize messenger RNA stability and translatability in host cells also are defined. The conditions for the use of a number of dominant drug selection markers for establishing permanent, stable cell clones expressing the products are also provided, as is an element that links expression of the drug selection markers to expression of the polypeptide.

Throughout this application, the term "expression construct" is meant to include any type of genetic construct containing a nucleic acid coding for a gene product in which part or all of the nucleic acid encoding sequence is capable of being transcribed. The transcript may be translated into a protein, but it need not be. In certain embodiments, expression includes both transcription of a gene and translation of mRNA into a gene product. In other embodiments, expression only includes transcription of the nucleic acid encoding a gene of interest.

In preferred embodiments, the nucleic acid encoding a gene product is under transcriptional control of a promoter. A "promoter" refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a gene. The phrase "under transcriptional control" means that the promoter is in the correct location and orientation in relation to the nucleic acid to control RNA polymerase initiation and expression of the gene. Typically, the promoter is selected for high level expression, such as *lac* inducible promoter for use in *E. coli*, alcohol oxidase for yeast, CMV IE for various mammalian systems, or the polyhedron promoter for Baculovirus. Other elements include polyadenylation signals, origins of replication, internal ribosome entry sites (IRES) and selectable markers (*e.g.*, neomycin, puromycin, hygromycin, DHFR, GPT, zeocin and histidinol).

Transfer of expression constructs into cells also is contemplated by the present invention. These include calcium phosphate precipitation (Graham and Van Der Eb, 1973; Chen and Okayama, 1987; Rippe *et al.*, 1990) DEAE-dextran (Gopal, 1985), electroporation (Tur-Kaspa *et al.*, 1986; Potter *et al.*, 1984), direct microinjection (Harland and Weintraub, 1985), DNA-loaded liposomes (Nicolau and Sene, 1982; Fraley *et al.*, 1979) and lipofectamine-DNA complexes, cell sonication (Fechheimer *et al.*, 1987), gene bombardment using high velocity microprojectiles (Yang *et al.*, 1990), and receptor-mediated transfection (Wu and Wu, 1987; Wu and Wu, 1988).

In certain embodiments of the invention, the expression construct comprises a virus or engineered construct derived from a viral genome. The ability of certain viruses to enter cells *via* receptor-mediated endocytosis, to integrate into host cell genome and express viral genes stably and efficiently have made them attractive candidates for the transfer of foreign genes into mammalian cells (Ridgeway, 1988; Nicolas and Rubenstein, 1988; Baichwal and Sugden, 1986; Temin, 1986). The first viruses used as gene vectors were DNA viruses including the papovaviruses (simian virus 40, bovine papilloma virus, and polyoma) (Ridgeway, 1988; Baichwal and Sugden, 1986) and adenoviruses (Ridgeway, 1988; Baichwal and Sugden, 1986). Retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins, making them attractive candidates for transformation of cells. Other viral vectors may be employed as expression constructs in the present invention. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Baichwal and Sugden, 1986; Coupar *et al.,* 1988) adeno-associated virus (AAV) (Ridgeway, 1988; Baichwal and Sugden, 1986; Hermonat and Muzycska, 1984) and herpesviruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Baichwal and Sugden, 1986; Coupar *et al.,* 1988; Horwich *et al.,* 1990).

In a further embodiment of the invention, the expression construct (and PAGs) may be entrapped in a liposome. Liposomes are vesicular structures characterized by a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh and Bachhawat, 1991).

IV. Generating Antibodies Reactive With PAGs

In another aspect, the present invention contemplates an antibody that is immunoreactive with a PAG molecule of the present invention, or any portion thereof. An antibody can be a polyclonal or a monoclonal antibody composition, both of which are preferred embodiments of the present invention. Means for preparing and characterizing antibodies are well known in the art (see, *e.g.*, Harlow and Lane, 1988).

Briefly, a polyclonal antibody is prepared by immunizing an animal with an immunogen comprising a peptide or polypeptide of the present invention and collecting antisera from that immunized animal. A wide range of animal species can be used for the production of antisera. Typically an animal used for production of anti-antisera is a non-human animal including rabbits, mice, rats, hamsters, pigs or horses. Because of the relatively large blood volume of rabbits, a rabbit is a preferred choice for production of polyclonal antibodies.

Antibodies, both polyclonal and monoclonal, specific for isoforms of antigen may be prepared using conventional immunization techniques, as will be generally known to those of skill in the art. A composition containing antigenic epitopes of the compounds of the present invention can be used to immunize one or more experimental animals, such as a rabbit or mouse, which will then proceed to produce specific antibodies against the compounds of the present invention. Polyclonal antisera may be obtained, after allowing time for antibody generation, simply by bleeding the animal and preparing serum samples from the whole blood.

It is proposed that the monoclonal antibodies of the present invention will find useful application in standard immunochemical procedures, such as ELISA and Western blot methods and in immunohistochemical procedures such as tissue staining, as well as in other procedures which may utilize antibodies specific to PAG-related antigen epitopes. Additionally, it is proposed that monoclonal antibodies specific to the particular PAG of different species may be utilized in other useful applications.

In general, both polyclonal and monoclonal antibodies against PAG may be used in a variety of embodiments. For example, they may be employed in antibody cloning protocols to obtain cDNAs or genes encoding other PAG polypeptides. They may also be used in inhibition studies to analyze the effects of PAG related peptides in cells or animals. Anti-PAG antibodies will also be useful in immunolocalization studies to analyze the distribution of PAG polypeptides during various cellular events, for example, to determine the cellular or tissue-specific distribution of PAG polypeptides under different points in the cell cycle. A particularly useful application of such antibodies is in purifying native or recombinant PAG, for example, using an antibody affinity column. The operation of all such immunological techniques will be known to those of skill in the art in light of the present disclosure.

Means for preparing and characterizing antibodies are well known in the art (see, *e.g.*, Harlow and Lane, 1988; incorporated herein by reference). More specific examples of monoclonal antibody preparation are give in the examples below.

As is well known in the art, a given composition may vary in its immunogenicity. It is often necessary therefore to boost the host immune system, as may be achieved by coupling a peptide or polypeptide immunogen to a carrier. Exemplary and preferred carriers are keyhole limpet hemocyanin (KLH) and bovine serum albumin (BSA). Other albumins such as ovalbumin, mouse serum albumin or rabbit serum albumin can also be used as carriers. Means for conjugating a polypeptide to a carrier protein are well known in the art and include glutaraldehyde, *m*-maleimidobencoyl-N-hydroxysuccinimide ester, carbodiimide and bis-biazotized benzidine.

As also is well known in the art, the immunogenicity of a particular immunogen composition can be enhanced by the use of non-specific stimulators of the immune response, known as adjuvants. Exemplary and preferred adjuvants include complete Freund's adjuvant (a non-specific stimulator of the immune response containing killed

Mycobacterium tuberculosis), incomplete Freund's adjuvants and aluminum hydroxide adjuvant.

The amount of immunogen composition used in the production of polyclonal antibodies varies upon the nature of the immunogen as well as the animal used for immunization. A variety of routes can be used to administer the immunogen (subcutaneous, intramuscular, intradermal, intravenous and intraperitoneal). The production of polyclonal antibodies may be monitored by sampling blood of the immunized animal at various points following immunization. A second, booster, injection may also be given. The process of boosting and titering is repeated until a suitable titer is achieved. When a desired level of immunogenicity is obtained, the immunized animal can be bled and the serum isolated and stored, and/or the animal can be used to generate mAbs.

MAbs may be readily prepared through use of well-known techniques, such as those exemplified in U.S. Patent 4,196,265, incorporated herein by reference. Typically, this technique involves immunizing a suitable animal with a selected immunogen composition, *e.g.*, a purified or partially purified PAG. The immunizing composition is administered in a manner effective to stimulate antibody producing cells. Rodents such as mice and rats are preferred animals, however, the use of rabbit, sheep or frog cells is also possible. The use of rats may provide certain advantages (Goding, 1986), but mice are preferred, with the BALB/c mouse being most preferred as this is most routinely used and generally gives a higher percentage of stable fusions.

Following immunization, somatic cells with the potential for producing antibodies, specifically B-lymphocytes (B-cells), are selected for use in the mAb generating protocol. These cells may be obtained from biopsied spleens, tonsils or lymph nodes, or from a peripheral blood sample. Spleen cells and peripheral blood cells are preferred, the former because they are a rich source of antibody-producing cells that are in the dividing plasmablast stage, and the latter because peripheral blood is easily

accessible. Often, a panel of animals will have been immunized and the spleen of animal with the highest antibody titer will be removed and the spleen lymphocytes obtained by homogenizing the spleen with a syringe. Typically, a spleen from an immunized mouse contains approximately 5×10^7 to 2×10^8 lymphocytes.

The antibody-producing B lymphocytes from the immunized animal are then fused with cells of an immortal myeloma cell, generally one of the same species as the animal that was immunized. Myeloma cell lines suited for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render then incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas).

Any one of a number of myeloma cells may be used, as are known to those of skill in the art (Goding, 1986; Campbell, 1984). For example, where the immunized animal is a mouse, one may use P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bul; for rats, one may use R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210; and U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6 are all useful in connection with cell fusions.

Methods for generating hybrids of antibody-producing spleen or lymph node cells and myeloma cells usually comprise mixing somatic cells with myeloma cells in a 2:1 ratio, though the ratio may vary from about 20:1 to about 1:1, respectively, in the presence of an agent or agents (chemical or electrical) that promote the fusion of cell membranes. Fusion methods using Sendai virus have been described (Kohler and Milstein, 1975; 1976), and those using polyethylene glycol (PEG), such as 37% (v/v) PEG, by Gefter *et al.*, (1977). The use of electrically induced fusion methods is also appropriate (Goding, 1986).

Fusion procedures usually produce viable hybrids at low frequencies, around 1×10^{-6} to 1×10^{-8}. However, this does not pose a problem, as the viable, fused hybrids

are differentiated from the parental, unfused cells (particularly the unfused myeloma cells that would normally continue to divide indefinitely) by culturing in a selective medium. The selective medium is generally one that contains an agent that blocks the *de novo* synthesis of nucleotides in the tissue culture media. Exemplary and preferred agents are aminopterin, methotrexate, and azaserine. Aminopterin and methotrexate block *de novo* synthesis of both purines and pyrimidines, whereas azaserine blocks only purine synthesis. Where aminopterin or methotrexate is used, the media is supplemented with hypoxanthine and thymidine as a source of nucleotides (HAT medium). Where azaserine is used, the media is supplemented with hypoxanthine.

The preferred selection medium is HAT. Only cells capable of operating nucleotide salvage pathways are able to survive in HAT medium. The myeloma cells are defective in key enzymes of the salvage pathway, *e.g.*, hypoxanthine phosphoribosyl transferase (HPRT), and they cannot survive. The B-cells can operate this pathway, but they have a limited life span in culture and generally die within about two weeks. Therefore, the only cells that can survive in the selective media are those hybrids formed from myeloma and B-cells.

This culturing provides a population of hybridomas from which specific hybridomas are selected. Typically, selection of hybridomas is performed by culturing the cells by single-clone dilution in microtiter plates, followed by testing the individual clonal supernatants (after about two to three weeks) for the desired reactivity. The assay should be sensitive, simple and rapid, such as radioimmunoassays, enzyme immunoassays, cytotoxicity assays, plaque assays, dot immunobinding assays, and the like.

The selected hybridomas would then be serially diluted and cloned into individual antibody-producing cell lines, which clones can then be propagated indefinitely to provide mAbs. The cell lines may be exploited for mAb production in two basic ways. A sample of the hybridoma can be injected (often into the peritoneal cavity) into a

histocompatible animal of the type that was used to provide the somatic and myeloma cells for the original fusion. The injected animal develops tumors secreting the specific monoclonal antibody produced by the fused cell hybrid. The body fluids of the animal, such as serum or ascites fluid, can then be tapped to provide mAbs in high concentration. The individual cell lines could also be cultured *in vitro*, where the mAbs are naturally secreted into the culture medium from which they can be readily obtained in high concentrations. mAbs produced by either means may be further purified, if desired, using filtration, centrifugation and various chromatographic methods such as HPLC or affinity chromatography.

V. Assays for PAG Expression in the Detection of Pregnancy

According to the present invention, the present inventors have determined that certain PAGs are advantageously expressed in early stages of pregnancy and, therefore, can be used as markers in the detection of pregnancy at an early stage. While the present invention is exemplifed in cattle, its extension to other species including sheep (*e.g.* deer, antelopes, and giraffes), horses (*Perissodactyla*), and all other ruminant ungulates and even more distantly related species (dogs, cats, humans) is contemplated. In addition, the immunoassays, may be qualitative or quantitative.

In cattle, the boPAGs may be used individually or in combination to provide a diagnostic evaluation of pregnancy. According to the present invention, these boPAGs include BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21. Other boPAGs, and PAGs from other species, may prove useful, alone or in combination, for similar purposes.

A. Immunologic Detection of Pregnancy

The present invention entails the use of antibodies in the immunologic detection of PAGs. Various useful immunodetection methods have been described in the scientific

literature, such as, *e.g.*, Nakamura *et al.* (1987; incorporated herein by reference). Immunoassays, in their most simple and direct sense, are binding assays. Certain preferred immunoassays are the various types of enzyme linked immunosorbent assays (ELISAs) and radioimmunoassays (RIA). Immunohistochemical detection using tissue sections also is particularly useful. However, it will be readily appreciated that detection is not limited to such techniques, and Western blotting, dot blotting, FACS analyses, and the like also may be used in connection with the present invention.

In general, immunobinding methods include obtaining a sample suspected of containing a protein, peptide or antibody, and contacting the sample with an antibody or protein or peptide in accordance with the present invention, as the case may be, under conditions effective to allow the formation of immunocomplexes. Preferred samples, according to the present invention, are fluids, such as milk, urine, blood, serum or saliva.

Contacting the chosen biological sample with the protein, peptide or antibody under conditions effective and for a period of time sufficient to allow the formation of immune complexes (primary immune complexes) is generally a matter of simply adding the composition to the sample and incubating the mixture for a period of time long enough for the antibodies to form immune complexes with PAGs. After this time, the PAG-antibody mixture will be washed to remove any non-specifically bound antibody species, allowing only those antibodies specifically bound within the primary immune complexes to be detected.

In general, the detection of immunocomplex formation is well known in the art and may be achieved through the application of numerous approaches. These methods are generally based upon the detection of a label or marker, such as any radioactive, fluorescent, biological or enzymatic tags or labels of standard use in the art. U.S. Patents concerning the use of such labels include 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149 and 4,366,241, each incorporated herein by reference. Of course,

one may find additional advantages through the use of a secondary binding ligand such as a second antibody or a biotin/avidin ligand binding arrangement, as is known in the art.

Usually, the primary immune complexes may be detected by means of a second binding ligand that has binding affinity for the PAG or the PAG-specific first antibody. In these cases, the second binding ligand may be linked to a detectable label. The second binding ligand is itself often an antibody, which may thus be termed a "secondary" antibody. The primary immune complexes are contacted with the labeled, secondary binding ligand, or antibody, under conditions effective and for a period of time sufficient to allow the formation of secondary immune complexes. The secondary immune complexes are then generally washed to remove any non-specifically bound labeled secondary antibodies or ligands, and the remaining label in the secondary immune complexes is then detected.

Further methods include the detection of primary immune complexes by a two step approach. A second binding ligand, such as an antibody, that has binding affinity for the PAG or anti-PAG antibody is used to form secondary immune complexes, as described above. The second binding ligand contains an enzyme capable of processing a substrate to a detectable product and, hence, amplifying signal over time. After washing, the secondary immune complexes are contacted with substrate, permitting detection.

B. ELISA

As a part of the practice of the present invention, the principles of an enzyme-linked immunoassay (ELISA) may be used. ELISA was first introduced by Engvall and Perlmann (1971) and has become a powerful analytical tool using a variety of protocols (Engvall, 1980; Engvall, 1976; Engvall, 1977; Gripenberg *et al.*, 1978; Makler *et al.*, 1981; Sarngadharan *et al.*, 1984). ELISA allows for substances to be passively adsorbed to solid supports such as plastic to enable facile handling under laboratory conditions. For a comprehensive treatise on ELISA the skilled artisan is referred to "ELISA; Theory and Practise" (Crowther, 1995 incorporated herein by reference).

The sensitivity of ELISA methods is dependent on the turnover of the enzyme used and the ease of detection of the product of the enzyme reaction. Enhancement of the sensitivity of these assay systems can be achieved by the use of fluorescent and radioactive substrates for the enzymes. Immunoassays encompassed by the present invention include, but are not limited to those described in U.S. Patent 4,367,110 (double monoclonal antibody sandwich assay) and U.S. Patent 4,452,901 (western blot). Other assays include immunoprecipitation of labeled ligands and immunocytochemistry, both *in vitro* and *in vivo*.

In a preferred embodiment, the invention comprises a "sandwich" ELISA, where anti-PAG antibodies are immobilized onto a selected surface, such as a well in a polystyrene microtiter plate or a dipstick. Then, a test composition suspected of containing PAGs, *e.g.*, a clinical sample, is contacted with the surface. After binding and washing to remove non-specifically bound immunocomplexes, the bound antigen may be detected by a second antibody to the PAG.

In another exemplary ELISA, polypeptides from the sample are immobilized onto a surface and then contacted with the anti-PAG antibodies. After binding and washing to remove non-specifically bound immune complexes, the bound antibody is detected. Where the initial antibodies are linked to a detectable label, the primary immune complexes may be detected directly. Alternatively, the immune complexes may be detected using a second antibody that has binding affinity for the first antibody, with the second antibody being linked to a detectable label.

Another ELISA in which the PAGs are immobilized involves the use of antibody competition in the detection. In this ELISA, labeled antibodies are added to the wells, allowed to bind to the PAG, and detected by means of their label. The amount of PAG in a sample is determined by mixing the sample with the labeled antibodies before or during

incubation with coated wells. The presence of PAG in the sample acts to reduce the amount of antibody available for binding to the well, and thus reduces the ultimate signal.

Irrespective of the format employed, ELISAs have certain features in common, such as coating, incubating or binding, washing to remove non-specifically bound species, and detecting the bound immune complexes. In coating a plate with either antigen or antibody, one will generally incubate the wells of the plate with a solution of the antigen or antibody, either overnight or for a specified period of hours. The wells of the plate will then be washed to remove incompletely adsorbed material. Any remaining available surfaces of the wells are then "coated" with a nonspecific protein that is antigenically neutral with regard to the test antisera. These include bovine serum albumin (BSA), casein and solutions of milk powder. The coating allows for blocking of nonspecific adsorption sites on the immobilizing surface and thus reduces the background caused by nonspecific binding of antisera onto the surface.

In ELISAs, it is probably more customary to use a secondary or tertiary detection means rather than a direct procedure. Thus, after binding of a protein or antibody to the well, coating with a non-reactive material to reduce background, and washing to remove unbound material, the immobilizing surface is contacted with the control human cancer and/or clinical or biological sample to be tested under conditions effective to allow immune complex (antigen/antibody) formation. Detection of the immune complex then requires a labeled secondary binding ligand or antibody, or a secondary binding ligand or antibody in conjunction with a labeled tertiary antibody or third binding ligand.

"Under conditions effective to allow immune complex (antigen/antibody) formation" means that the conditions preferably include diluting the antigens and antibodies with solutions such as BSA, bovine gamma globulin (BGG), evaporated or powdered milk, and phosphate buffered saline (PBS)/Tween. These added agents also tend to assist in the reduction of nonspecific background.

The "suitable" conditions also mean that the incubation is at a temperature and for a period of time sufficient to allow effective binding. Incubation steps are typically from about 1h to 2h to 4 h, at temperatures preferably on the order of 25°C to 27°C, or may be overnight at about 4°C or so.

To provide a detecting means, the second or third antibody will have an associated label to allow detection. Preferably, this will be an enzyme that will generate color development upon incubating with an appropriate chromogenic substrate. Thus, for example, one will desire to contact and incubate the first or second immune complex with a urease, glucose oxidase, alkaline phosphatase or hydrogen peroxidase-conjugated antibody for a period of time and under conditions that favor the development of further immunecomplex formation (*e.g.*, incubation for 2 h at room temperature in a PBS-containing solution such as PBS-Tween).

After incubation with the labeled antibody, and subsequent to washing to remove unbound material, the amount of label is quantified, *e.g.*, by incubation with a chromogenic substrate such as urea and bromocresol purple or 2,2'-azido-di-(3-ethyl-benzthiazoline-6-sulfonic acid [ABTS] and H_2O_2, in the case of peroxidase as the enzyme label. Quantitation is then achieved by measuring the degree of color generation, *e.g.*, using a visible spectra spectrophotometer.

A variant of ELISA is the enzyme-linked coagulation assay, or ELCA (U.S. Patent 4,668,621), which uses the coagulation cascade combined with the labeling enzyme RVV-XA as a universal detection system. The advantage of this system for the current invention, is that the coagulation reactions can be performed at physiological pH in the presence of a wide variety of buffers. It is therefore possible to retain the integrity of complex analytes.

C. Immunohistochemistry

While primarily useful in research contexts, immunohistochemistry may be useful according to the present invention in identifying new PAGs. This involves testing of both fresh-frozen and formalin-fixed, paraffin-embedded tissue blocks prepared from study by immunohistochemistry (IHC). For example, each tissue block consists of 50 mg of residual "pulverized" placental tissue. The method of preparing tissue blocks from these particulate specimens has been successfully used in previous IHC studies of various prognostic factors, *e.g.*, in breast, and is well known to those of skill in the art (Brown *et al.*, 1990; Abbondanzo *et al.*, 1990; Allred *et al.*, 1990).

Briefly, frozen-sections may be prepared by rehydrating 50 ng of frozen "pulverized" placental tissue at room temperature in phosphate buffered saline (PBS) in small plastic capsules; pelleting the particles by centrifugation; resuspending them in a viscous embedding medium (OCT); inverting the capsule and pelleting again by centrifugation; snap-freezing in -70°C isopentane; cutting the plastic capsule and removing the frozen cylinder of tissue; securing the tissue cylinder on a cryostat microtome chuck; and cutting 25-50 serial sections containing an average of about 500 remarkably intact placental cells.

Permanent-sections may be prepared by a similar method involving rehydration of the 50 mg sample in a plastic microfuge tube; pelleting; resuspending in 10% formalin for 4 h fixation; washing/pelleting; resuspending in warm 2.5% agar; pelleting; cooling in ice water to harden the agar; removing the tissue/agar block from the tube; infiltrating and embedding the block in paraffin; and cutting up to 50 serial permanent sections.

D. Immunodetection Kits

In further embodiments, the invention provides immunological kits for use in detecting PAGs in biological samples. Such kits will generally comprise one or more PAGs or PAG-binding proteins that have immunospecificity for various PAGs and for antibodies. More specifically, the immunodetection kits will thus comprise, in suitable

container means, one or more PAGs, antibodies that bind to PAGs, and antibodies that bind to other antibodies *via* Fc portions.

In certain embodiments, the PAG or primary anti-PAG antibody may be provided bound to a solid support, such as a column matrix or well of a microtitre plate. Alternatively, the support may be provided as a separate element of the kit.

The immunodetection reagents of the kit may include detectable labels that are associated with, or linked to, the given antibody or PAG itself. Detectable labels that are associated with or attached to a secondary binding ligand are also contemplated. Such detectable labels include chemilluminescent or fluorescent molecules (rhodamine, fluorescein, green fluorescent protein, luciferase), radioabels (^{3}H, ^{35}S, ^{32}P, ^{14}C, ^{131}I) or enzymes (alkaline phosphatase, horseradish peroxidase).

The kits may further comprise suitable standards of predetermined amounts, including both antibodies and PAGs. These may be used to prepare a standard curve for a detection assay.

The kits of the invention, regardless of type, will generally comprise one or more containers into which the biological agents are placed and, preferably, suitable aliquoted. The components of the kits may be packaged either in aqueous media or in lyophilized form.

The container means of the kits will generally include at least one vial, test tube, flask, bottle, or even syringe or other container means, into which the antibody or antigen may be placed, and preferably, suitably aliquoted. Where a second or third binding ligand or additional component is provided, the kit will also generally contain a second, third or other additional container into which this ligand or component may be placed.

The kits of the present invention will also typically include a means for containing the antibody, PAG and any other reagent containers in close confinement for commercial

sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained.

VI. Methods for Identifying Additional PAGs

By following the basic teachings of the examples, it will be possible to identify additional PAGs and, further, correlate their expression with early and late stage pregnancy. This is done by obtaining various tissues (*e.g.*, placenta) as described in the examples and detecting the presence of various PAG transcripts therein. One of the best known nucleic acid amplification methods is the polymerase chain reaction (referred to as PCR™) which is described in detail in U.S. Patents 4,683,195, 4,683,202 and 4,800,159, and in Innis *et al.*, 1990, each of which is incorporated herein by reference in its entirety. These methods may be applied directly to the identification of PAGs.

Briefly, in PCR™, two primer sequences are prepared that are complementary to regions on opposite complementary strands of the marker sequence. An excess of deoxynucleoside triphosphates are added to a reaction mixture along with a DNA polymerase, *e.g.*, *Taq* polymerase. If the marker sequence is present in a sample, the primers will bind to the marker and the polymerase will cause the primers to be extended along the marker sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the marker to form reaction products, excess primers will bind to the marker and to the reaction products and the process is repeated.

Where transcripts are the nucleic acid sample of interest, a reverse transcriptase (RT)-PCR™ amplification procedure may be performed in order to convert the mRNA transcript to DNA and then amplify it for detection or cloning. Methods of reverse transcribing RNA into cDNA are well known and described in Sambrook *et al.*, 1989. Alternative methods for reverse transcription utilize thermostable, RNA-dependent DNA polymerases. These methods are described in WO 90/07641 filed December 21, 1990. Polymerase chain reaction methodologies are well known in the art.

Using PAG-related sequences as primers for either reverse transcription or for amplification, one may selectively amplify PAGs from these samples. Alternatively, one may simply create a cDNA library and screen the library using standard probing formats (*e.g.*, Southern blotting). Identified clones may then be sequenced. Partial clones coding for less than a full length transcripts can, in turn, be used to isolate the complete sequence from other cDNA or even genomic libraries.

VII. <u>Examples</u>

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

A. Example 1. Cloning of boPAGs from Placental Tissues early in Pregnancy

<u>Materials and Methods:</u> Bovine PAG transcripts were cloned from day 19 and 25 placentae. RNA from six (Simmental × Hereford) placentas at day 25 of pregnancy was used to construct a cDNA library in λZAPII (Clontech, Palo Alto, CA). The library was screened with a mixed probe of ^{32}P-labeled bovine, ovine and porcine PAG1 and PAG2, and equine PAG cDNA (Xie *et al.*, 1991, Xie *et al.*, 1994; Xie *et al.*, 1995; Szafranska *et al.*, 1995). The positive clones were isolated and analyzed for the size of inserts by PCR™ and restriction endonuclease digestion. Sixteen clones of the expected length were partially sequenced. The second screening identified boPAG transcripts that reacted with an anti-boPAG1 antiserum (Zoli *et al.*, 1991; Xie *et al.*, 1991). Duplicate filter screening was employed to increase the frequency of isolation of full length clones. The

first filter was allowed to react with antiserum to identify immunopositive clones (Xie *et al.*, 1991), while the second filter was hybridized with a ^{32}P- labeled probe corresponding to exons 1 and 2 of boPAG1, ovPAG1 and ovPAG2. The clones positive on both filters were purified and partially sequenced.

PAG transcripts from a day 19 trophoblast of a Holstein cow were cloned by reverse transcription (RT) and PCR™ procedures. Cellular RNA, extracted from day 19 trophoblast, was first reverse transcribed into cDNA then amplified by PCR™ with a pair of well-conserved primers (boPAGexp3′5′ CCCAAGCTTATGAAGTGGCTTGTGCTCCT3′ (SEQ ID NO:16), and boPAGexp3′ 5′GGGAAGCTTACTTGTCATCGTCGTCCTTGTAGTCGGTACCCACCTGTGCCAG GCCAATCCTGTCATTTC3′ (SEQ ID NO:17). The RT-PCR™ products were cloned into TA cloning vectors (Invitrogen, CA USA). All the novel boPAG cDNAs were fully sequenced.

Results: Alignment of amino acid sequences of all boPAG available is shown in FIG. 1. BoPAG1, 2 and 3 have been identified previously at Day 260 of pregnancy, *i.e.*, close to term (Xie *et al*, 1991; Xie *et al.*, 1994; Xie *et al.*, 1995) and are, therefore, "late" PAGs. Transcripts for boPAGs 4, 5, 6, 7, 8, 9, 10 and bo PAG11 (SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11) were all present in the day 25 library (FIG. 3). BoPAG12 (SEQ ID NO:12) was present in the day 19 Holstein placenta (FIG. 3). All these are, therefore, "early" PAGs and candidates for early pregnancy antigens. Note that PAG2 (SEQ ID NO:2), previously detected in late pregnancy (Xie *et al.*, 1994), is also present at day 19 and 25, but that boPAG1 (SEQ ID NO:1) is not expressed on any of these days as determined by a combination of procedures, including immuno screening. This point is important as the antisera used by others for detecting pregnancy (Sasser *et al.*, 1986; Zoli *et al.*, 1992a; Mialon *et al.*, 1993) appear to recognize boPAG1. Note also that the antiserum against boPAG1 does recognize one of the "early" PAGs, namely PAG4. It seems likely, therefore, that these previous investigators were able to detect early

pregnancy in cows because their antiserum fortuitously cross-reacted, albeit weakly, with boPAG4.

A considerable degree of amino acid sequence identity exists among the 12 boPAGs listed in FIG. 1. The most related are boPAG1 and boPAG3, sharing a 86% amino acid identity. The least related are boPAG4 and boPAG10 with only 49% identity. Interestingly boPAG1 and boPAG4, which as noted above cross react with the anti-boPAG1 antiserum, exhibit only 76% identity at the amino acid level. Presumably a common epitope exists on the two molecules.

The hypervariable regions noted in FIG. 1 coincide with surface loop regions on the modeled structures (Xie *et al*, 1997b) and are potential distinguishing epitopes. In this regard, boPAG1 and boPAG4 share one common loop (LSKDEREGS:209-217; PAG1 numbering) (FIG. 1), which may explain their immunological cross reactivity. Other loops could be mimicked as synthetic peptides and used to immunize rabbits or mice in order to raise specific antibodies against particular PAGs.

These data show that boPAG1, the antigen used as the basis for previous pregnancy tests, is a "late" PAG and not ideal as an early pregnancy antigen. The data also show that the "early" PAGs are relatively numerous and differ considerably from each other and from boPAG1 in sequence. These differences are most marked in surface loop regions, which are likely to be the most immunoreactive features of the molecule.

B. Example 2. Structural relationships among boPAGS

Materials and Methods: The amino acid sequences of various PAGs and pepsin were assembled into multiple sequence alignments with the Pile Up Program of the Wisconsin GCG Package, Version 9.0 (Madison, WI). A distance matrix was then created (Program Distances) and a phylogenetic tree constructed by a neighbor-joining procedure (Nei, 1987).

Results: The data in FIG. 5 is a phylogenetic tree relating all of the bovine PAGs (FIG. 1) and ovine PAGs (FIG. 2) that have so far been cloned as cDNA. The methods used for cloning these PAG cDNAs is described by Xie *et al.*, 1997b. Also included in FIG. 5 are rabbit pepsinogen F and porcine pepsinogen A, the aspartic proteinases structurally most similar to PAGs. Note that the bovine and ovine PAGs fall largely into two structurally related groups. One contains boPAG2, -10, -11, and -12, along with ovPAG2 and ovPAG5. The other is comprised of boPAG1, 3, 4, 5, 6, 7, and 9. As pointed out below and by Xie *et al.,* (1997b) the boPAGs in this second group are expressed only in binucleate cells, the invasive component of the trophoblast and the cell type considered to release PAGs into the maternal bloodstream. Note that among the PAGs in the second group are the "early" PAGs, boPAG4, 5, 6, 7, and 9.

C. Example 3. Certain early PAGs are expressed in trophoblast binucleate cells and in the syncytium formed between trophectoderm and uterine epithelium.

Materials and Methods: Riboprobes (cRNA) were prepared by using the Riboprobe Preparation System (Promega, WI, USA). Briefly, two regions of the boPAG cDNA, representing poorly conserved sequences, were used as the probe *in situ* hybridization (and ribonuclease protection assay: see next section). The first fragment (536bp) of boPAG2, 4, 8, 9 or 11 cDNA, that was in the region of exons 6, 7, 8 and 9, was amplified by using PCR™ with a pair of primers (Forward 5′CCTCTTTTGCCTTCTACTTGA3′ (SEQ ID NO:18, and Reverse 5′GCGCTCGAGTTACACTGCCCGTGCCAGGC3′ (SEQ ID NO:19). However, another region (407bp) was chosen for boPAG1, 5, 6 and 7 cDNA, corresponding to exons 3, 4 and 5. Again it was amplified by a PCR™ procedure with two well conserved primers (Forward B: 5′TGGGTAACATCACCATTGGAA3′ (SEQ ID NO:20, Reverse B: 5′TTTCTGAGCCTGTTTTTGCC5′ (SEQ ID NO:21). The PCR™ products were subcloned into TA cloning vectors (Invitrogen, CA, USA). The orientation and sequence of the inserts were determined by sequencing.

The subcloned cDNA fragments were then transcribed *in vitro* into cRNA in the presence of [^{35}S]-CTP. Non-incorporated [^{35}S]CTP was removed by centrifugation of the labeling mix through a Sephadex G-50 column. The control probes, sense cRNA of boPAG, were prepared in essentially the way described above. The probes were used within 3 days. Day 25 or Day 100 tissue was sectioned (14μm) at -18 °C with an IEC cryostat (International Equipment Co., Needham Heights, MA) and mounted onto prechilled microscope slides.

The sections were then fixed and processed as described by Xu *et al.,* (1995). Hybridization was performed by application of about 200μl of probe solutions (4x10^6 cpm) to cover each section and incubated at 55°C for 12 to 18 h. After hybridization, the slides were dipped in 2X SSC to remove the excess hybridization buffer, treated with RNase A(50μl/ml in PBS) for 30 min at 37°C to eliminate probes that were not hybridized. The sections were then washed at 55°C in 2X SSC for 15 min, in 50% formamide in 2X SSC for 30 min and twice in 0.1X SSC for 15 min. Slides were again dehydrated, air dried, coated with Kodak NTB-2 emulsion (Eastman Kodak, Rochester, NY) and exposed for 1 to 4 weeks at 4°C. Finally, the slides were developed, counterstained with hematoxylin and eosin and examined microscopically.

In situ hybridization was performed with [^{35}S]-antisense probes on sections through placentomes (areas of fused cotyledonary, *i.e.*, fetal and caruncular, *i.e.*, maternal, villi). Resulting autoradiographs were stained with hemotoxylin and cosin and photographed. No specific hybridization signals were shown with sense probe. BoPAG9 mRNA was concentrated in the more scattered binucleate cells, while that for boPAG11 was found in all the cells of the chorionic epithelium (trophectoderm).

In situ hybridization was performed with [^{35}S]-antisense probes on day 25 endometrium-placental sections using darkfield micrographs at 20X and 40X. The silver-grains appear to be white dots under darkground illumination. The cell layer at the edge of the section gave an intense boPAG6 signal. Abundant silver stains were localized to

the cells at the margin of the section. In contrast, boPAG2 mRNA gave only a weak signal within the syncytial region. Few silver grains were visible at the edge of the section.

Results:

1. *Localization of boPAG mRNAs at Day 100 of Pregnancy*

The outer layer of the placenta consists of two populations of trophoblast cells, mono- and binucleate trophoblast cells. To localize the site of each PAG expression specifically to mono- or binucleate trophoblast cells, *in situ* hybridization were performed to detect individual PAG mRNA. Previous published data have shown that while boPAG1 is expressed in trophoblast binucleate cells (Xie *et al.*, 1994), boPAG2 is expressed throughout the trophectoderm, including the more abundant mononucleated cells that comprise 80% or more of the epithelium (Xie *et al.*, 1994).

Here, *in situ* hybridization has been on sections of placentomes employed to determine in what cell type the remaining characterized boPAGs are expressed. BoPAG9 is expressed largely in the scattered binucleate cells, which are heavily covered with silver grains. By contrast, mRNA for boPAG11 is found throughout the epithelium covering the cotyledonary villi.

There is a correspondence between the PAGs that are expressed in binucleate cells and their positions in the phylogenetic tree (FIG. 5), and that four of the PAGs known to be expressed early, namely boPAG4, 5, 6, 7 and 9, are produced by the invasive binucleate cell, and therefore, likely to enter the maternal bloodstream.

2. *Localization at Day 25 of Pregnancy*

Bovine placenta on day 25 of pregnancy is not fully developed and the cotyledons are not firmly interdigitated with the caruncular endometrium. Therefore, the thickened placental membrane was processed with the attached endometrium. By the time it had been through the *in situ* hybridization procedures, most of the membrane was lost. Only

the layer that fused with the endometrium survived the harsh procedure and remained on the surface of endometrium.

It was very difficult to identify individual cells since most cells (the remaining placental tissue) were fused with the underlining endometrial cells. Nevertheless, these fused multicellular syncytium contained plentiful amount of boPAG6 mRNA. As observed previously, only binucleate trophoblast can fuse with endometrium. Therefore, the placental cells in the syncytium are most likely to be binucleate trophoblast cells in origin. Similarly the sections hybridized to boPAG4, 5, 7 and 9 probes, also had very strong signals at the interface between the remaining placental membrane and the endometrial epithelium. Hence, they are most likely to be expressed by the binucleate trophoblast cells.

In contrast, very little mRNA for boPAG2, 8, 10, 11 was localized to the syncytical layer. A plausible explanation is that either those boPAG are not expressed or are expressed at low levels in the fused binucleate trophoblast cells at day 25 placenta. They are less likely, therefore, to be found in maternal blood than boPAG4, 5, 6, 7 and 9.

D. Example 4. Relative Expression of mRNA for different boPAG transcripts varies over gestation in cows.

Materials and Methods: Riboprobes (cRNA) were prepared by the Riboprobe Preparation System (Promega, WI, USA). Briefly, two regions of the boPAG cDNA, that represent poorly conserved regions of PAGs in general were used as probes for RPA as well as for *in situ* hybridization. The first fragment (536 bp) of boPAG2, 4, 8, 9 and 11 cDNA, in the region of exons 6, 7, 8 and 9, was amplified by using PCR™ with the same pair of primers (SEQ ID NO:18 and SEQ ID NO:19) described in Example 3 for *in situ* hybridization. Similarly a region (407 bp) of boPAG1, 5, 6, or 7 cDNA corresponding to exons 3, 4 and 5, was amplified as described in Example 3 with primers (SEQ ID NO:20 and SEQ ID NO:21).

After subcloning, the cDNA fragments were transcribed *in vitro* into cRNA in the presence of [^{32}P-α]CTP. Total cellular RNA was extracted from placental tissue at different stages of pregnancy by using guanidium.isothiocyanate and purified over a cesium chloride gradient (Sambrook *et al.*, 1989; Ausubel *et al*, 1987). Twenty μg of RNA was used for each RPA reaction according to the manufacturer's recommendations (Ambion Inc., Austin, Texas). In short, the sample RNA was co-precipitated with ^{32}P-labeled probes 2x10^{6} cpm/sample) and the pellet suspended in 10μl of hybridization buffer and incubated at 68°C for 10 min. Unhybridized cRNA was digested with a mixture of RNase A/T1 for 45 min at 37°C. The cRNA probe and mRNA hybrids were precipitated and separated in 6% long range sequence gels and visualized by autoradiography.

A fragment of boPAG cDNA was amplified by PCR™ and the products subsequently subcloned into TA cloning vectors. Those fragments were then *in vitro* transcribed into riboprobes in the presence [^{32}P] CTP. RNA was extracted from bovine conceptus and placenta on days 25, 45, 88, 250 and term of pregnancy. The total tissue RNA (20 μm) was then hybridized with cRNA probes of boPAG1, boPAG2, boPAG4, boPAG5, boPAG6, boPAG7, boPAG8, boPAG9, boPAG10 and boPAG11. The protected DNA fragments were separated and visualized by autoradiography.

Results: The length of gestation in cattle is about 285 days. Initial immunoscreening of cDNA libraries previously identified three boPAG (boPAG1, 2 and 3). More recently two additional cDNA (boPAG13 and boPAG14) were cloned from mRNa of term placenta by using hybridization screening (SEQ ID NO:13) and (SEQ ID NO:14) in a day 260 placental cDNA library (Xie *et al*, 1991; Xie *et al.*, 1995). On day 25 pregnancy, ten distant PAG were identified (Example 1, FIG. 1, FIG. 2 and FIG. 5). Only boPAG2 was isolated from both stages of pregnancy. These cloning data imply that expression of individual boPAG is temporally controlled. To confirm the temporal expression of boPAG, ribonuclease protection assays were carried out to delineate the stages at which individual boPAGgenes were expressed in the cattle placenta. This

procedure was repeated at least twice for each boPAG riboprobe and for each RNA sample. The major band represents the protected boPAG mRNA. In addition, there were multiple small bands in each lane. Those smaller bands almost certainly protected sequences highly related to, but distinct from, that of the riboprobe.

In summary boPAG2, was found in RNA at days 19, 25 and 260 and was therefore expressed through gestation. Similarly boPAG8, 10 and 11 were expressed at all stages of pregnancy examined. BoPAG1, which was originally characterized from day 260 placenta and is the basis of the pregnancy test of Sasser *et al.,* (1986), Zoli *et al*, (1992a) and Mialon *et al*, (1992; 1993) was expressed at a very low level on day 25 of pregnancy. By day 45, its expression was elevated markedly. Other boPAG in the same group had varied expression on day 25. However, none of them showed enhanced expression by day 45 of pregnancy.

E. Example 5. Artiodactyla species related to Bos taurus also have multiple PAG genes.

<u>Materials and Methods</u>: Southern genomic blots of bovine DNA were performed with probes corresponding to a segment of the boPAG1 encompassing part of intron 6, exon 7, intron 7, exon 8 the proximal end and the proximal end of intron 8 (Xie *et al.*, 1995). The restriction enzyme *Eco*R1 was chosen that did not cleave the probe. Conditions of hybridization were such that the PAG1 probe did not bind the PAG2 gene, nor would there be hybridization to genes for other known aspartic proteinases.

<u>Results</u>: Multiple PAG genes were detectable in all species of the *Bovidae* family examined. Signals were especially strong in the species closely related to *Bos taurus* within the subfamilies *Bovinae (e.g., Bos frontalis gaurus,* gaur; *Bos grunniens,* yak: *Syncerus caffer,* Cape buffalo) and *Caprinae (e.g., Ovis aires,* domestic sheep; *ovis dalli,* Dall sheep; *Capra falconeri,* Markhor goat, *Nemorhaedus goral*, goral; *Budorcas taxicolor,* takin). Gazelle and antelope species in other related subfamilies, including the impala, gnu, duiker, and nyala, also gave strong signals.

In general hybridization, although detectable, was weaker to DNA of members of the *Cervidae* family, including the whitetail deer and mule deer, than to DNA from *Bovidae*. Unexpectedly, moose (*Alces alces*) gave a relatively strong signal. The giraffe (family *Giraffidae*) provided the weakest signal of the true pecoran ruminants, possibly reflecting its early divergence (Kageyama *et al.*, 1990). Hybridization to DNA from the Nile hippopotamus was barely detectable with the boPAG1 probe employed. since the hippo (family *Hippotamidae*; suborder *Suiformes*) is related to the domestic pig (*Sus Scrofa*), a species with multiple PAGs (Szafranska *et al.*, 1995), this result indicates the considerable divergence of the genes within the Artiodactyla order over the 55 to 65 million years of its existence.

These data together show that there are multiple PAG genes with considerable structural similarity to boPAG1 in all ruminant ungulate species examined. Thus, a pregnancy test developed for domestic cattle (*Bos taurus*) on the basis of "early" PAG secretion by the placenta might also have utility in these other species as well.

F. Example 6. The placenta of the domestic cat (Feli catus) expresses a PAG related to boPAGs.

Materials and Methods: Day 30 cat placentas from a single litter were obtained from the University of Missouri Veterinary Taching Hospital. Tissue was cut into small chunks and frozen in liquid N_2. Total RNA was extracted from frozen tissues and polyA$^+$ mRNA purified by using the micro-FastTrack™ kit from Invitrogen, CA. This RNA was reverse transcribed and the resulting cDNA collected ( ). PCR™ was conducted with the following primers, which represent highly conserved regions of the majority of boPAG genes (5′TGGGTAACATCACCATTGGAAC3′ (215-236), (SEQ ID NO:22, ovPAGe5r 5′CAAACATCACCACACTGCCCTCC3′ (667-645), (SEQ ID NO:23).

PCR™ reactions were run for 35 cycles. Each cycle was 94°C for 1 min.; 42°C for 1 min.; 72°C for 1 min. The *TA cloning kit* (Invitrogen, CA) was employed to clone

the PCR™ products. Plasmid DNA was isolated by using a *Mini Prep Kit* (Promega, Madison, WI). The isolated plasmid DNA were digested with the *Eco*RI restriction enzyme to check the sizes of inserts. In order to localize the site of cat PAG expression more precisely, *in situ* hybridization (as described in Example 3, section C) was used to detect cat PAG mRNA in frozen day 30 cat placental tissue. Cat PAG transcripts were detected with an antisense ^{35}S-labeled riboprobe.

<u>Results</u>: The open reading frame of the cat PAG cDNA was 1164bp and encoded a polypeptide of 388 amino acids with a predicted Mr of 43,035 Cat PAG (SEQ ID NO:15). The amino acid sequence (SEQ ID NO:38) of cat PAG showed between 50 and 60% identity to all known bovine PAGs and 59.4% identity to porcine pepsinogen A.

Together these data suggest that the PAG occur outside the Ungulata order and are also found in non-hoofed species such as the domestic cat. By inference they are likely to be also found in related cat species (*Felidae*) as well as in the dogs (*Canidae*). A pregnancy test based on "early" PAG antigens could have utility in these species, particularly in the domestic dog (*Canis familiarus)*.

* * * * * * * * * * * * * * * *

All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications

apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

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WHAT IS CLAIMED IS:

1. A method for detecting pregnancy in a bovine animal comprising:

(a) obtaining a sample from said animal; and

(b) detecting at least one pregnancy associated antigen (PAG) wherein said PAG is present in early pregnancy and absent at about two months post-partum;

whereby the presence of the PAG indicates that said animal is pregnant.

2. The method of claim 1, wherein said PAG is selected from the group consisting of PAG2, PAG4, PAG5, PAG6, PAG7 and PAG9.

3. The method of claim 1, wherein said sample is saliva, serum, blood, milk or urine.

4. The method of claim 3, wherein said sample is saliva.

5. The method of claim 3, wherein said sample is serum.

6. The method of claim 3, wherein said sample is blood.

7. The method of claim 3, wherein said sample is milk.

8. The method of claim 3, wherein said sample is urine.

9. The method of claim 1, wherein said detecting comprises immunologic detection.

10. The method of claim 9, wherein said immunologic detection comprises detection of BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v;

boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21 with polyclonal antisera.

11. The method of claim 9, wherein said immunologic detection comprises detection of BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21 with a monoclonal antibody preparation.

12. The method of claim 9, wherein said immunologic detection comprises ELISA.

13. The method of claim 9, wherein said immunologic detection comprises RIA.

14. The method of claim 9, wherein said immunologic detection comprises Western blot.

15. The method of claim 3, wherein the PAG is BoPAG2.

16. The method of claim 3, wherein the PAG is BoPAG4.

17. The method of claim 3, wherein the PAG is BoPAG5.

18. The method of claim 3, wherein the PAG is BoPAG6.

19. The method of claim 3, wherein the PAG is BoPAG7.

20. The method of claim 3, wherein the PAG is BoPAG9.

21. The method of claim 3, wherein the PAG is BoPAG7v.

22. The method of claim 3, wherein the PAG is BoPAG9v.

23. The method of claim 3, wherein the PAG is BoPAG15.

24. The method of claim 3, wherein the PAG is BoPAG16.

25. The method of claim 3, wherein the PAG is BoPAG17.

26. The method of claim 3, wherein the PAG is BoPAG18.

27. The method of claim 3, wherein the PAG is BoPAG19.

28. The method of claim 3, wherein the PAG is BoPAG20.

29. The method of claim 3, wherein the PAG is BoPAG21.

30. The method of claim 1, further comprising detecting a second PAG in said sample.

31. The method of claim 30, further comprising detecting a third PAG in said sample.

32. The method of claim 12, wherein said ELISA is a sandwich ELISA comprising binding of a PAG to a first antibody preparation fixed to a substrate and a second antibody preparation labeled with an enzyme.

33. The method of claim 32, wherein said enzyme is alkaline phosphatase or horseradish peroxidase.

34. The method of claim 32, wherein said first antibody preparation is monoclonal.

35. An antibody composition that reacts immunologically with BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21.

36. An antibody composition that reacts immunologically with BoPAG2.

37. An antibody composition that reacts immunologically with BoPAG4.

38. An antibody composition that reacts immunologically with BoPAG5.

39. An antibody composition that reacts immunologically with BoPAG6.

40. An antibody composition that reacts immunologically with BoPAG7.

41. An antibody composition that reacts immunologically with BoPAG9.

42. An antibody composition that reacts immunologically with BoPAG7v.

43. An antibody composition that reacts immunologically with BoPAG9v.

44. An antibody composition that reacts immunologically with BoPAG15.

45. An antibody composition that reacts immunologically with BoPAG16.

46. An antibody composition that reacts immunologically with BoPAG17.

47. An antibody composition that reacts immunologically with BoPAG18.

48. An antibody composition that reacts immunologically with BoPAG19.

49. An antibody composition that reacts immunologically with BoPAG20.

50. An antibody composition that reacts immunologically with BoPAG21.

51. A hybridoma cell that secretes a monoclonal antibody that reacts immunologically with BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21.

52. A method of making a monoclonal antibody to BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21 comprising:

(a) immunizing an animal with a BoPAG preparation;
(b) obtaining antibody secreting cells from said immunized animal;
(c) immortalizing said antibody secreting cells; and
(d) identifying an immortalized cell that secretes antibodies that bind immunologically with the immunizing BoPAG.

53. A method of identifying a pregnancy associated glycoprotein (PAG) that is an early indicator of pregnancy in an Eutherian animal comprising:

(a) obtaining a cDNA library prepared from the placenta of said animal between days 15 and 30 of pregnancy; and
(b) hybridizing said library under high stringency conditions with a PAG-derived nucleic acid probe;

whereby hybridization of said probe identifies said PAG.

54. A method of identifying a pregnancy associated glycoprotein (PAG) that is an early indicator of pregnancy in an Eutherian animal comprising:

(a) obtaining an RNA preparation from the placenta of said animal between days 15 and 30 of pregnancy; and
(b) performing RT- PCR™ on said preparation using PAG-derived primers;

whereby amplification identifies said PAG.

55. An isolated and purified BoPAG2 polypeptide.

56. The polypeptide of claim 55, wherein said polypeptide comprises the sequence of SEQ ID NO:25.

57. An isolated and purified BoPAG4 polypeptide.

58. The polypeptide of claim 57, wherein said polypeptide comprises the sequence of SEQ ID NO:27.

59. An isolated and purified BoPAG5 polypeptide.

60. The polypeptide of claim 59, wherein said polypeptide comprises the sequence of SEQ ID NO:28.

61. An isolated and purified BoPAG6 polypeptide.

62. The polypeptide of claim 61, wherein said polypeptide comprises the sequence of SEQ ID NO:29.

63. An isolated and purified BoPAG7 polypeptide.

64. The polypeptide of claim 63, wherein said polypeptide comprises the sequence of SEQ ID NO:30.

65. An isolated and purified BoPAG9 polypeptide.

66. The polypeptide of claim 65, wherein said polypeptide comprises the sequence of SEQ ID NO:32.

67. An isolated and purified BoPAG7v polypeptide.

68. The polypeptide of claim 67, wherein said polypeptide comprises the sequence of SEQ ID NO:40.

69. An isolated and purified BoPAG9v polypeptide.

70. The polypeptide of claim 69, wherein said polypeptide comprises the sequence of SEQ ID NO:42.

71. An isolated and purified BoPAG15 polypeptide.

72. The polypeptide of claim 71, wherein said polypeptide comprises the sequence of SEQ ID NO:44.

73. An isolated and purified BoPAG16 polypeptide.

74. The polypeptide of claim 73, wherein said polypeptide comprises the sequence of SEQ ID NO:46.

75. An isolated and purified BoPAG17 polypeptide.

76. The polypeptide of claim 75, wherein said polypeptide comprises the sequence of SEQ ID NO:48.

77. An isolated and purified BoPAG18 polypeptide.

78. The polypeptide of claim 77, wherein said polypeptide comprises the sequence of SEQ ID NO:50.

79. An isolated and purified BoPAG19 polypeptide.

80. The polypeptide of claim 79, wherein said polypeptide comprises the sequence of SEQ ID NO:52.

81. An isolated and purified BoPAG20 polypeptide.

82. The polypeptide of claim 81, wherein said polypeptide comprises the sequence of SEQ ID NO:54.

83. An isolated and purified BoPAG21 polypeptide.

84. The polypeptide of claim 83, wherein said polypeptide comprises the sequence of SEQ ID NO:56.

85. An isolated and purified nucleic acid encoding BoPAG2.

86. The nucleic acid of claim 85, wherein said nucleic acid comprises the sequence of SEQ ID NO:2

87. The nucleic acid of claim 85, wherein said nucleic acid encodes a BoPAG2 polypeptide comprising the sequence of SEQ ID NO:25.

88. An isolated and purified nucleic acid encoding BoPAG4.

89. The nucleic acid of claim 88, wherein said nucleic acid comprises the sequence of SEQ ID NO:4

90. The nucleic acid of claim 88, wherein said nucleic acid encodes a BoPAG4 polypeptide comprising the sequence of SEQ ID NO:27.

91. An isolated and purified nucleic acid encoding BoPAG5.

92. The nucleic acid of claim 91, wherein said nucleic acid comprises the sequence of SEQ ID NO:5.

93. The nucleic acid of claim 91, wherein said nucleic acid encodes a BoPAG5 polypeptide comprising the sequence of SEQ ID NO:28.

94. An isolated and purified nucleic acid encoding BoPAG6.

95. The nucleic acid of claim 94, wherein said nucleic acid comprises the sequence of SEQ ID NO:6.

96. The nucleic acid of claim 94, wherein said nucleic acid encodes a BoPAG6 polypeptide comprising the sequence of SEQ ID NO:29.

97. An isolated and purified nucleic acid encoding BoPAG7.

98. The nucleic acid of claim 97, wherein said nucleic acid comprises the sequence of SEQ ID NO:7.

99. The nucleic acid of claim 97, wherein said nucleci acid encodes a BoPAG7 polypeptide comprising the sequence of SEQ ID NO:30.

100. An isolated and purified nucleic acid encoding BoPAG9.

101. The nucleic acid of claim 100, wherein said nucleic acid comprises the sequence of SEQ ID NO:9.

102. The nucleic acid of claim 100, wherein said nucleic acid encodes a BoPAG9 polypeptide comprising the sequence of SEQ ID NO:32.

103. An isolated and purified nucleic acid encoding BoPAG7v.

104. The nucleic acid of claim 103, wherein said nucleic acid comprises the sequence of SEQ ID NO:39.

105. The nucleic acid of claim 103, wherein said nucleci acid encodes a BoPAG7v polypeptide comprising the sequence of SEQ ID NO:40.

106. An isolated and purified nucleic acid encoding BoPAG9v.

107. The nucleic acid of claim 106, wherein said nucleic acid comprises the sequence of SEQ ID NO:41.

108. The nucleic acid of claim 106, wherein said nucleci acid encodes a BoPAG9v polypeptide comprising the sequence of SEQ ID NO:42.

109. An isolated and purified nucleic acid encoding BoPAG15.

110. The nucleic acid of claim 109, wherein said nucleic acid comprises the sequence of SEQ ID NO:43.

111. The nucleic acid of claim 109, wherein said nucleci acid encodes a BoPAG15 polypeptide comprising the sequence of SEQ ID NO:44.

112. An isolated and purified nucleic acid encoding BoPAG16.

113. The nucleic acid of claim 112, wherein said nucleic acid comprises the sequence of SEQ ID NO:45.

114. The nucleic acid of claim 112, wherein said nucleci acid encodes a BoPAG16 polypeptide comprising the sequence of SEQ ID NO:46.

115. An isolated and purified nucleic acid encoding BoPAG17.

116. The nucleic acid of claim 115, wherein said nucleic acid comprises the sequence of SEQ ID NO:47.

117. The nucleic acid of claim 115, wherein said nucleci acid encodes a BoPAG17 polypeptide comprising the sequence of SEQ ID NO:48.

118. An isolated and purified nucleic acid encoding BoPAG18.

119. The nucleic acid of claim 118, wherein said nucleic acid comprises the sequence of SEQ ID NO:49.

120. The nucleic acid of claim 118, wherein said nucleci acid encodes a BoPAG18 polypeptide comprising the sequence of SEQ ID NO:50.

121. An isolated and purified nucleic acid encoding BoPAG19.

122. The nucleic acid of claim 121, wherein said nucleic acid comprises the sequence of SEQ ID NO:51.

123. The nucleic acid of claim 121, wherein said nucleci acid encodes a BoPAG19 polypeptide comprising the sequence of SEQ ID NO:52.

124. An isolated and purified nucleic acid encoding BoPAG20.

125. The nucleic acid of claim 124, wherein said nucleic acid comprises the sequence of SEQ ID NO:53.

126. The nucleic acid of claim 124, wherein said nucleci acid encodes a BoPAG20 polypeptide comprising the sequence of SEQ ID NO:54.

127. An isolated and purified nucleic acid encoding BoPAG21.

128. The nucleic acid of claim 127, wherein said nucleic acid comprises the sequence of SEQ ID NO:55.

129. The nucleic acid of claim 127, wherein said nucleci acid encodes a BoPAG21 polypeptide comprising the sequence of SEQ ID NO:56.

130. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:9, or the complement thereof.

131. The oligonucleotide of claim 130, wherein said oligonucleotide is about 20 bases in length.

132. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:7, or the complement thereof.

133. The oligonucleotide of claim 132, wherein said oligonucleotide is about 20 bases in length.

134. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:6, or the complement thereof.

135. The oligonucleotide of claim 134, wherein said oligonucleotide is about 20 bases in length.

136. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:5, or the complement thereof.

137. The oligonucleotide of claim 136, wherein said oligonucleotide is about 20 bases in length.

138. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:4, or the complement thereof.

139. The oligonucleotide of claim 138, wherein said oligonucleotide is about 20 bases in length.

140. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:2 or the complement thereof.

141. The oligonucleotide of claim 140, wherein said oligonucleotide is about 20 bases in length.

142. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:39 or the complement thereof.

143. The oligonucleotide of claim 142, wherein said oligonucleotide is about 20 bases in length.

144. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:41 or the complement thereof.

145. The oligonucleotide of claim 144, wherein said oligonucleotide is about 20 bases in length.

146. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:43 or the complement thereof.

147. The oligonucleotide of claim 146, wherein said oligonucleotide is about 20 bases in length.

148. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:45 or the complement thereof.

149. The oligonucleotide of claim 148, wherein said oligonucleotide is about 20 bases in length.

150. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:47 or the complement thereof.

151. The oligonucleotide of claim 150, wherein said oligonucleotide is about 20 bases in length.

152. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:49 or the complement thereof.

153. The oligonucleotide of claim 152, wherein said oligonucleotide is about 20 bases in length.

154. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:51 or the complement thereof.

155. The oligonucleotide of claim 154, wherein said oligonucleotide is about 20 bases in length.

156. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:53 or the complement thereof.

157. The oligonucleotide of claim 156, wherein said oligonucleotide is about 20 bases in length.

158. An oligonucleotide comprising at least about 15 consecutive bases of the sequence of SEQ ID NO:55 or the complement thereof.

159. The oligonucleotide of claim 158, wherein said oligonucleotide is about 20 bases in length.

160. A kit comprising:

(a) a first monoclonal antibody preparation that binds immunologically to BoPAG2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, boPAG 7v; boPAG9v; boPAG 15; boPAG 16; boPAG 17; boPAG 18; boPAG 19; boPAG 20 or boPAG 21; and

(b) a suitable container means therefor.

161. The kit of claim 160, further comprising:

(c) a second monoclonal antibody preparation that binds immunologically to the same BoPAG as said first monoclonal antibody, but wherein said first and said second monoclonal antibodies bind to different epitopes; and

(d) a suitable container means therefor.

162. The kit of claim 161, wherein said first antibody preparation is attached to a support.

163. The kit of claim 162, wherein said support is a polystyrene plate, test tube or dipstick.

164. The kit of claim 161, wherein said second antibody preparation comprises a detectable label.

165. The kit of claim 164, wherein said detectable label is a fluorescent tag.

166. The kit of claim 164, wherein said detectable label is a chemilluminescent tag.

167. The kit of claim 164, wherein said detectable label is an enzyme.

168. The kit of claim 167, wherein said enzyme is alkaline phosphatase or horseradish peroxidase.

169. The kit of claim 167, further comprising a substrate for said enzyme.

170. The kit of claim 161, further comprising:

(e) a buffer or diluent; and

(f) a suitable container means therefor.

171. A method for detecting pregnancy in a non-bovine Eutherian animal comprising:

(a) obtaining a sample from said animal; and

(b) detecting at least one of pregnancy associated antigen (PAG) in said sample, wherein said PAG is present in early pregnancy,

whereby the presence of the PAG indicates that said animal is pregnant.

172. The method of claim 171, wherein said animal is a member of the suborder *Ruminantia*.

173. The method of claim 172, wherein said animal is a member of the family *Bovidae*.

174. The method of claim 173, wherein said animal is a goat or sheep.

175. The method of claim 174, wherein said animal is a sheep.

176. The method of claim 172, wherein said animal is a member of the order *Perissodactyla*.

177. The method of claim 176, wherein said animal is a horse or rhinoceros.

178. The method of claim 177, wherein said animal is a horse.

179. The method of claim 171, wherein said animal is a member of the order *Carnivora*.

180. The method of claim 179, wherein said animal is a dog or cat.

181. The method of claim 179, wherein said animal is a human.

ABSTRACT

Pregnancy-associated glycoproteins (PAGs) are structurally related to the pepsins, thought to be restricted to the hoofed (ungulate) mammals and characterized by being expressed specifically in the outer epithelial cell layer (chorion/trophectoderm) of the placenta. By cloning expressed genes from ovine and bovine placental cDNA libraries, the inventors estimate that cattle, sheep, and most probably all ruminant Artiodactyla, possess possibly 100 or more PAG genes, many of which are placentally expressed. The PAGs are highly diverse in sequence, with regions of hypervariability confined largely to surface-exposed loops. Selected PAG that are products of the i0nvasive binucleate cells, expressed highly in early pregnancy at the time of trophoblast invasion and expressed weakly, if at all, in late gestation are useful in the early diagnosis of pregnancy. In a preferred embodiment, the invention relates to immunoassays for detecting these PAGs.

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                                                                   ▼ (1)
Consensus   MKWLVLLGLV AFSECIVKIP LR..KTMR.T LS.KN.LNNF LKE.AYRLSQ IS.RGSNLT-    60  (2)

boPAG 8     .......... .L........ .TKM...QEA IRE.QL.ED. .D.QPHS... H.DPDKKFS.    59
boPAG 2     .......... .L.....IL. .KKM..L.E. .RE..L.... .E.Q.....K N---D.KI..    56
boPAG12     .......... .L.....IL. ..KM..L.E. .RE. L..... .E.R.....K K---D.KI..    56
boPAG11     .....F.... .......IML .TKT....EI WRE.KL..S. .E.Q.N.M.D D.ASDPK.S.    59
boPAG 9     ...I...... .......... ..QV....K. ..G..M.K.. ...HP..... ..F.......    59
boPAG10     ....G..... .L...M.I.. ..QM....E. .RERHL.T.. SE.HP.N... KAANDQ.IIY    60
boPAG 4     .......... .......... ..RV...TK. ..G..M.... V..H...... ..F.......    59
boPAG 6     .......... .......... ..RV....NA I.G..T...I ...H....P. ..F.......    59
boPAG 1     .......... .......... ..RL....NV V.G..M.... ...H..S... ..F.......    59
boPAG 3     .DD....... .......... ..RV...N. V.G..I...I ...HV..... ..F.......    59
boPAG 5     .........L TS.....IL. .TKV....K. ..E..M.... ...Q...... ..S....I..    59
boPAG 7     .......... .......... ..RV....K. ..G..M.... ...DP....H ..F.......    59

Consensus   .HPLRNI.D. .YVGNITIGT PPQEFQVVFD TGSSDLWVPS I.C.S.AC.T H.RFRH..SS   120  (62)

boPAG 8     S.Q.K.FQNA V.F.T..... ......N... .......... VD.Q.PS.SK .K..DPQK.T   119
boPAG 2     I.....YL.T A......... ......R... ...AN....C .T.T.P..Y. .KT.NPQN..   116
boPAG12     I...K.YL.M A......... ......R... ...A...... .S.V.P..Y. .KT.NLHN..   116
boPAG11     T.....AL.M A......... ..K..R.... .......... .K.I.P..H. .IT.D.HK..   119
boPAG 9     I......MNL V......... .......... .......... FCTM-P..SA PVW..QLQ..   118
boPAG10     H....SYK.F S.I...N... ......L... ....S..... .Y.Q.SS.YK .NS.VPCN..   120
boPAG 4     I......R.F .......... ......I... ....E..... .F.N.ST.SK .D....LE..   119
boPAG 6     -......R.L F......... ......I... ........A. .F.N.SS.AA .V....HQ..   118
boPAG 1     T......K.L V.M....... ......I... .A........ DF.T.P..S. .V....LQ..   119
boPAG 3     T......K.L I......... .......... .....F.... DF.T.R..S. .V....LQ..   119
boPAG 5     I......M.M V...K..... .......... ....E..... VF.P.S..S. .I....LE..   119
boPAG 7     I......R.I F......... ......I... .......... .D.N.TS.A. .V....LQ..   119

Consensus   TFR.TNKTF. I.YGSG.MKG .L..DTVRIG .LVSTDQPFG LS.EE-.GF. ...-.DGVLG   180 (120)

boPAG 8     ..QPL.QKIE LV....T... V.GS..IQ.. N..IVN.I.. ..QNQSS.VL EQVPY..I..   179
boPAG 2     S..EVGSPIT .F....IIQ. F.GS...... N...PE.S.. ..L...Y..D SLP.F..I..   174
boPAG12     S.GQ.HQPIS .S..P.IIQ. F.GS...... N...LK.S.. ..Q...Y..D GAP.F.....   174
boPAG11     ...L.RRP.H .L....M.N. V.AY...... K......... ..LQQ.F..D NAP.F.....   177
boPAG 9     ..QP.....T .T....S... F.AY...... D......... ..VV..Y.LE GRN.Y.....   176
boPAG10     ..KA...I.N TN.TATSI.. Y.VY...... N...VA.... ..LK..F..D DVP.F..I..   178
boPAG 4     ...LSRR..S .T....RIEA LVVH...... D......Q.. .CL...S..E GMR.F.....   177
boPAG 6     ...P.....R .T....R... VVVH...... D......... .CLKD.S..K GIP.F..I..   176
boPAG 1     ...L.....R .T....R... VVVH...... N......... ..I...Y..E GRI.Y.....   177
boPAG 3     ...L.....R .T....R... VVAH...... D......... ..V...Y..E GRAYY.....   178
boPAG 5     .SGL.Q...S .T....ST.. F.AY...... D.L....E.. ..M...H..E DLPF-.....   177
boPAG 7     ...P.....R .I....R.N. VIAY...... D......... ..V...Y..A HKRF-..I..   177

Consensus   L.YP..S..G AIPIFDNLKN QGAISEPVFA FYLS....EG SVVMFGGVDH .YYKGELNW.   240 (180)

boPAG 8     .A..SLAIQ. TT.V...... REV....... ....SRPENI .T........ T.H..K.Q.I   239
boPAG 2     .AF.AMGIED T.......WS H..F...... ...NTNKP.. .......... R........I   234
boPAG12     .A..SI.IK. I.......WS ...F...... ...NTCQP.. .......... R........I   234
boPAG11     .S..SLAVP. T.....K..Q .......I.. ....TRKEN. ..L.L..... S.H..K...I   237
boPAG 9     .N..NI.FS. .......... .......... ....KNKQ.. .......... Q........I   236
boPAG10     .G..RRTIT. .N.....WK ..V....... ....SQKEN. ........NR A........V   238
boPAG 4     .S.TNI.PS. ......YK... E......... ....KDER.. .......A.. R........I   237
boPAG 6     .S..NKTFS. .F....K... E......... ....KDKQ.. .......... R........V   236
boPAG 1     .N..NI.FS. ......K... .R........ ....KDER.. .......... R..E.....V   237
boPAG 3     .N..NI.FS. .......... .......... IL..KDEQ.. .......... R..E.....V   238
boPAG 5     .N..DM.FIT T......... ...F...... ...GKVK--. .......... T........V   235
boPAG 7     .N.WNL.WSK .M....K... E......... ....NI---- ---------- ----------   213

Consensus   P..Q.G.W.. .MDRISM.R. VIACS.GC.A LVDTGTS.I. GP.RLV.NI. KLI.A.P-.G   300 (239)

boPAG 8     .VT.ARF.QV A.SSMT.NGN .VG..Q..Q. V......LLV ..TH..TD.L ...NPN.ILN   299
boPAG 2     .VS.TSH.QI S.NN...NGT .T...C..E. .L.....M.Y ..TK..T..H ..MN.RL.EN   293
boPAG12     .VS.TRY.QI S.N....NGN .T...R..Q. .L.....M.H ..T..IT..H ..MN.RH.Q.   293
boPAG11     .VS.TKS.LI TV.....NGR ..G.EH..E. .......L.H ..A.P.T..Q .F.H.M..Y.   296
boPAG 9     .LIEA.E.RV H......K.T .....D..E. ..H....H.E ..G...N..H R..RTR..FD   295
boPAG10     .VS.V.S.HI NI.S...NGT .V..KR..Q. SWIR.-RLSA W.K.I.SK.Q ...H.R..ID   296
boPAG 4     .LMKA.D.SV H......K.K .....G..K. ......S.D.V ..ST..N..W ...G.T..Q.   296
boPAG 6     .LI.V.D.FV H...TT.K.K .....D..K. .......D.V ..ST..N..W ...R.R..L.   295
boPAG 1     .LI.A.D.SV H.....IE.K I....D..K. .......D.V ..R...N..H R..G.I..R.   296
boPAG 3     .LIEA.D.II H......K.K I....GS.E. I......A.E ..RK..NK.H ...G.R..RH   297
boPAG 5     .LI.A.E.SL H......K.K .....G..E. FY.....L.L ..R...N..Q ...G.T..Q.   294
boPAG 7     ---------- -----T.N.E .....E..A. ......SN.Q ..G..ID..Q RI.G.T..R.   257

Consensus   SE..VSC.AV ..LPSIIFTI NGI.YPVP.. AYI.KDSRG. C...F..... ---.-S..ET   360 (295)

boPAG 8     D.QML..D.I NS..TLLL.. ...V....PD Y..QRF.ERI .FIS.QGGTE ILKNLGTS..   359
boPAG 2     ..YV...D.. KT..PV..N. ...D..LRPQ ...I.IQN-S .RSV.QGGTE ...N..SLN.   348
boPAG12     ..YV...D.. KT..PV..N. ...D..L.PQ ...T.AQN-F .LSI.HGGTE ...T..SP..   348
boPAG11     ..YM.L.PVI SI..PV.... ...D.S..RE ...Q.I.NSL .LST.HGD-D ...T.---DQ   348
boPAG 9     .KHY...F.T KY....T.I. ...K..MTAR ...F.....R .YSA.KENTV ...R.TSR..   351
boPAG10     R.HV...Q.I GT..PAV... ...D.....AQ ...QSL.G-Y .FSN.LVRPQ ...RVNES..   352
boPAG 4     ..HY...S.. NS........ KSNN.R..GQ ...L.....R .FTA.KGHQQ ...S..ST.M   352
boPAG 6     PQYF...S.. NT........ ...N.RL.AR ...H.....R .YTA.KEHRF ...S..PI..   351
boPAG 1     ..HY.P.SE. NT....V... ...N....GR ...L..D..R .YTT.QENRV ...S..ST..   352
boPAG 3     .KYYI..S.. NT........ ...N..C.GR ..VL.....R .YSM.QENKV ...S..ST..   353
boPAG 5     ..HYI..F.. IS........ ...NI...AR ...H.....H .YPT.KENTV ...ST.-T..   350
boPAG 7     .KYY...S.. NI........ ..VN....PR ...L.....H .YTT.KEKRV ...RR.-T.S   313

Consensus   WILGDVFLRL YFSVFDRGND RIGLA.AV                                       386 (323)

boPAG 8     .......... ....Y....N .....P.A                                       387
boPAG 2     .....I...Q .......K.R .....P..                                       376
boPAG12     ....G....Q ........R.. S....-Q.                                      375
boPAG11     .......... ....Y....N .....P..                                       376
boPAG 9     .....A...R .......... .....R..                                       379
boPAG10     .......... .........N .....P..                                       380
boPAG 4     .......... ........RK. .....TK.                                      380
boPAG 6     .L.......R .......... .....R..                                       379
boPAG 1     .Y........ .......... .....R..                                       380
boPAG 3     .........V .......... .....R..                                       381
boPAG 5     .......... .......... .....QV-                                       377
boPAG 7     .V..E..... .......... .....RR.                                       341
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FIG. 1

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                                                                                    (1)
Consensus   MKWLVLLGLV AFSECIVKIP LRRVKTMRKT LSGKNMLNNF LKEHPYRLSQ ISFR.SNLTI   60  (3)

ovPAG4      .......... ......F... .......... ........DV ........P. ....G...I.   60
ovPAG7      .......... ......F.V. ...L...... ...N.....V ...Y....P. ....D..V..   60
ovPAG3      ......F... ........V. ...L...... ...N.I...V ...Y....P. ....D..V..   60
ovPAG6      .......... SI........ .......... ..E....... ....A..... ....G.....   60
ovPAG1      .......... .......... ........N. ....K..S.. ....A..... ....A.....   60
ovPAG5      ....SV.... RV....E... .MK.NV.QE. .NE.SL.... ..KY....A. N.T.N.KMAF   60
ovPAG9      .......... ........M. .........N P....M.... ....A..... ....GL...-   59
ovPAG2      .......W.. .L....IM.. .TKT...EI. .RE..L.... .E.QAN.M.D D.ASDPK.ST   60
ovPAG8      .......A.. ......I... .......SN. A......... ..K....... ....G....T   60

Consensus   HPLRN..D.. YVGNITIGTP PQEFQVVFDT GSSDLWVPS. FC.S.T---C S.H.RFRH.Q  120 (60)

ovPAG4      .....IR.TF .......... .....L.... ...V.....V L.N.S..... .I.V....L.  117
ovPAG7      L....MK.IF .......... .P.......S T........I .WN.S..... .TLV..K.R.  117
ovPAG3      L....MK.IF .......... .......... A........I ..N.S..... .TRV....R.  117
ovPAG6      .....TK.LV .L........ ......S... .........D ..AIEA.... .L.T....L.  117
ovPAG1      .....IM.ML .......... .......... .....L...I N.L.P.KRP. .KQDK.K.H.  120
ovPAG5      V.M..FL.LA ..P.M...RG GEQ.R..... .........N ..T.PA.... YS.IT.KYWE  117
ovPAG9      ...S.YI.ML .T........ ..K..I.... .........N ..T.PA.... .TQA...YR.  116
ovPAG2      .....AL.MA ....V..... .K..R..... .........I K.I.PA.... YT.IT.D.HK  117
ovPAG8      ...M.IW.LL .L........ ......L..R .........L L.N.S..... AK.VM...RL  117

Consensus   SSTFR.TNKT F.I.YG.G.M KGVVAHDTVR IGDLVSTDQP FGLS..E.GF ...PFDGVLG  180 (120)

ovPAG4      .....T.... .W.T..A.T. .......... ......I... ....MA.Y.. HGRR......  177
ovPAG7      .....T.... .W.T..A.T. .......... ......I... ....MA.Y.. MDRR...I..  177
ovPAG3      .....LA... .G.M..A.K. ....V..... .......... ....VV.S.. EHRQ......  177
ovPAG6      .....P..R. .S.T..C.TV ....V..... .......... ....TA.HVS RCT.......  177
ovPAG1      .....F..D. .R.YF.S.T. R.F....... .......... ...IFL.SWL D-I....I..  179
ovPAG5      ...Y.H.T.P .E.A..S.RI ..HL.Y..IQ ..N....... ....LV.Y.. NGL....I..  177
ovPAG9      .....L..R. .C.T..S.GL ..I....... ..N....... ...TLK.Y.. ENI.......  176
ovPAG2      .....L.RRP .R.L..S.M. N..L.Y.... ..N....... ....LQQF.. DNA.......  177
ovPAG8      ...Y.L.... .M.F.RV.KI E...VR.... .......A.T ....IA.T.. ENTTL..I..  177

Consensus   LNYP..S..G .IPIFDKLKN EGAISEPVFA FYLSKD.QEG SVVMFGGVDH .YYKGELNWV  240 (180)

ovPAG4      ....RQ.CCR PT........ Q......... ......E... .......... R.........  237
ovPAG7      ....RQ.CSK TKW......S Q......... ......E... .......... T.......SL  237
ovPAG3      ....NL.FSK T......... .......... ......E... .......... S....K....  237
ovPAG6      ....SI.FWS T......... .......... ......G... .......... R.........  237
ovPAG1      ....KI.FS. A......... ...F...... ...N..K... .......... R.........  239
ovPAG5      ....N-.IL. A.....N..K Q......I.. .....GTVN. ..L.L....K A........I  236
ovPAG9      ....NI.FS. AV........ ....L..... ..F...E... .......... R..E......  236
ovPAG2      .S..SLAVP. T........Q Q......I.. ....TNKEN. ..L.L..... S.H..K...I  237
ovPAG8      .S..NT.CF. A......... .......... ....N----- ---------- ----------  212

Consensus   PL..AGDW.I .VDRISM.R. VIACS.GC.A LVDTG.S.I. GP.RLVDNIQ KLIGA.P.G.  300 (240)

ovPAG4      ..VK.D..T. Q......R.E .....D..D. .L...A.F.H ..G..I.D.. ....SE.RDL  297
ovPAG7      ..VK.D..S. H......R.E .....D..D. .L...A.F.H ..G..I.D.. ....SEQRDF  297
ovPAG3      ..IK....SV R..S.T.K.E .....D..R. .....S.H.Q ..G..I..V. ....TM.Q.S  297
ovPAG6      ..IP..N.MV HM...YIE.N .....A..K. V....AAF.E ..KSQ...M. .F...R.R.S  297
ovPAG1      ..IHP.E.S. PL.....R.K .....G..E. ..G..T.L.L ..RTV.E... .H...TQQCF  299
ovPAG5      ..IRV...R. R..H...KGK L.G..G..E. .....P.L.N ..T...T... R....M.L.P  296
ovPAG9      ..TK....IV RL....IG.K .....GD.E. V....TAF.G ..RK..KK.. .....RRR.N  296
ovPAG2      .VSQTKS.L. T......NGK ..G.EH..E. .....T.L.H ..AGP.T... .F.H.V.YDS  297
ovPAG8      ---------. TMK.-----E .....D..R. .....S.H.Q ..G.....V. .H..TM.Q.S  258

Consensus   KHYVSCSAVN TLPSIIFTIN GINYPVPAQA YILK.S.G.C YT.F...RVR .STE.WVLGD  360 (300)

ovPAG4      ...I...... .......... .......... ....G.T.H. ..A.RAK... T...S.....  357
ovPAG7      ...I...... .......... .......... ....G.T.H. ..A.RAK... T...S.....  357
ovPAG3      M...P..... .......... .......... ....GFT.H. ..A.RAK... T...S.....  357
ovPAG6      .Y..P..V.. .......R.. S......GR. ....NHR.R. ..T.KENQWS P...I.I...  357
ovPAG1      EYF......Y A....V.... .......P.. .LV.D.R.Q. .SP.QVN.AN P.A.N.I...  359
ovPAG5      .......TI. I......... ....TL.... ....T.Q.G. F.T.KGA..F KHR.T.....  356
ovPAG9      .--------- ---------- ---------- ----DDA.R. S.T.QEN... L...S.L..N  323
ovPAG2      EYM...PVIS I..PV..... S.D.S...E. ..Q.I.NSL. LSS.HGDN-- --.DK.I...  353
ovPAG8      M...P..... .......... .......GR. ....DFR.R. ..N.KKKIA. TF..Y....E  318

Consensus   VFLRLYFSVF DRGNDRIGLA PAV                                           383 (323)

ovPAG4      .......... .......... ..M                                           380
ovPAG7      .......... .......... ..M                                           380
ovPAG3      .......... ...H...... R.G                                           380
ovPAG6      .......... ...H...... R..                                           380
ovPAG1      ....R..... .......... R..                                           382
ovPAG5      I........Y ..EHN..A.. Q.R                                           379
ovPAG9      ....V.L... .......... ...                                           346
ovPAG2      .........Y ....N..... ...                                           376
ovPAG8      P......... .......... ...                                           341
```

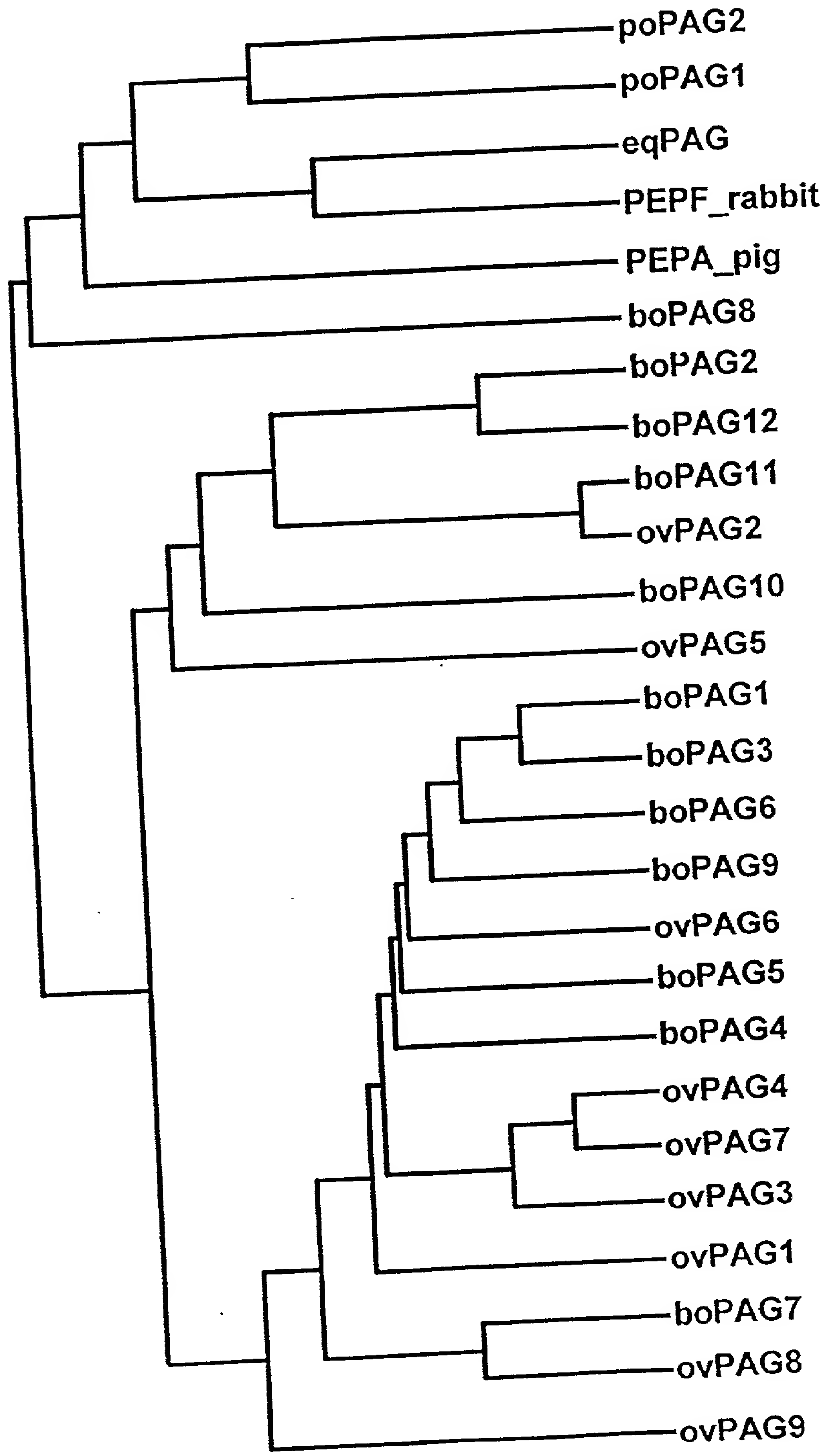
FIG. 2

boPAG	2	4	5	6	7	8	9	10	11	12
Hybrid(d25)	4		1	1	1	5	1	1	1	
Immuno(d25)		19								
RT-PCR(d19)	9					11	3		3	6

FIG. 3

BoPAG:	1	2	3	4	5	6	7	8	9	10	11	12
1	**100** 100											
2	**73** 57	**100** 100										
3	**91** 86	**74** 58	**100** 100									
4	**88** 76	**73** 55	**87** 73	**100** 100								
5	**86** 75	**60** 61	**86** 74	**85** 76	**100** 100							
6	**89** 80	**73** 57	**88** 78	**89** 76	**84** 70	**100** 100						
7	**87** 79	**73** 56	**87** 78	**86** 71	**85** 72	**89** 77	**100** 100					
8	**68** 53	**68** 55	**67** 51	**67** 49	**70** 54	**69** 53	**71** 53	**100** 100				
9	**87** 77	**74** 59	**88** 78	**85** 68	**85** 74	**87** 74	**86** 71	**68** 53	**100** 100			
10	**70** 56	**72** 50	**69** 55	**68** 53	**71** 58	**70** 57	**68** 53	**71** 55	**69** 57	**100** 100		
11	**74** 59	**77** 62	**73** 58	**73** 56	**76** 62	**73** 59	**75** 59	**72** 56	**73** 57	**72** 57	**100** 100	
12	**75** 61	**90** 83	**75** 60	**74** 58	**77** 63	**75** 59	**74** 58	**70** 56	**75** 60	**73** 60	**79** 64	**100** 100

FIG. 4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poPAG1
eqPAG
PEPF_rabbit
PEPA_pig
boPAG8
boPAG2
boPAG12
boPAG11
ovPAG2
boPAG10
ovPAG5
boPAG1
boPAG3
boPAG6
boPAG9
ovPAG6
boPAG5
boPAG4
ovPAG4
ovPAG7
ovPAG3
ovPAG1
boPAG7
ovPAG8
ovPAG9

FIG. 5

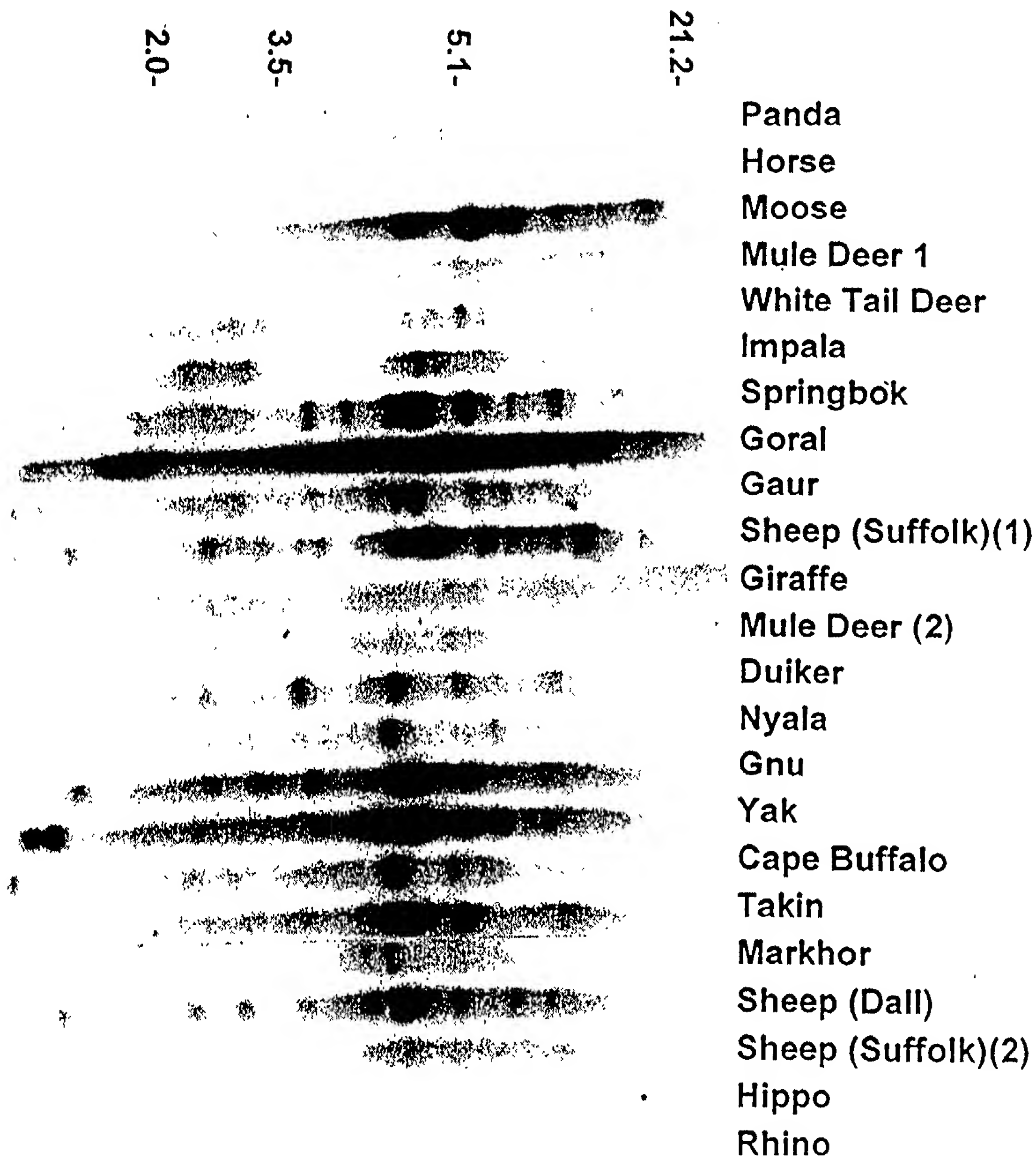
2.0-
3.5-
5.1-
21.2-
Panda
Horse
Moose
Mule Deer 1
White Tail Deer
Impala
Springbok
Goral
Gaur
Sheep (Suffolk)(1)
Giraffe
Mule Deer (2)
Duiker
Nyala
Gnu
Yak
Cape Buffalo
Takin
Markhor
Sheep (Dall)
Sheep (Suffolk)(2)
Hippo
Rhino

FIG. 6

<400> 15
aggaaagaag catgaagtgg ctttgggtcc ttgggctggt ggccctctca gagtgcttag 60
tcacaatccc tctgacgagg gtcaagtcca tgcgagaaaa cctcagggag aaagacaggc 120
tgaaggattt cctggagaac catccttaca acctggccta caagtttgtt gactctgtaa 180
atctggacct ggggatatat tttgaaccga tgaggaacta cctggatctg gcctacgttg 240
gcaccatcag cattggaacg cccccccagg agttcaaggt catctttgac accggctcat 300
ctgacttgtg ggtgccctcc atctactgct ctagccctgc ctgcgctaat cacaacgtct 360
tcaaccctct gcggtcctcc accttccgga tctcgggccg gcccatccac ctccagtacg 420
gctccgggac gatgtcagga tttctggcct acgacaccgt tcggttcggg ggcctcgttg 480
acgtggccca ggcgtttggc ctgagcctga gggagcccgg caagttcatg gaatacgcag 540
ttttcgacgg catcctgggc ctggcctacc ccagcctcag cctcagaggg accgtccctg 600
tcttcgacaa cctgtggaag cagggtctca tttctcagga gctctttgcc ttctacttga 660
gcaaaaagga cgaagaaggc agtgtggtga tgttcggcgg tgtggaccac tcctactaca 720
gcggagacct caactgggtg ccggtgtcca aacggctgta ctggcagtta tccatggaca 780
gcatctccat gaacggggaa gtcattgctt gtgacggtgg ctgccaggcc atcattgata 840
caggaacctc gctgctgatt ggcccatctc acgttgtctt caacatccag atgatcatcg 900
gcgccaacca gtcctacagc ggcgagtacg tagttgactg cgatgccgcc aacaccctgc 960
ccgacatcgt cttcaccatc aacggcatcg actacccggt gccagccagt gcctacatcc 1020
aggagggtcc tcagggcacc tgctacagcg gctttgacga gagcggagac agcttgttgg 1080
tctcagactc ctggatcctg ggcgatgtct tcctgaggtt gtatttcacc gtcttcgacc 1140
gagagaacaa caggattggc ctggccctgg cagtgtaaac actggggcca gctccaggaa 1200
gcaaccgtgc ccaccccaaa cccgcgcgcg cgtgtgcgca cacacacaca cacacacccc 1260
gcagtcaggg cattcctgcc caggggccgg cttgaactgt gtcttcggct ctgccaatcc 1320
cttctcccag tggagaataa aagacctcat cttccacggt 1360

<210> 16
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR primer

<400> 16
cccaagctta tgaagtggct tgtgctcct 29

<210> 17
<211> 69
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR primer

<400> 17
gggaagctta cttgtcatcg tcgtccttgt agtcggtacc cacctgtgcc aggccaatcc 60
tgtcatttc 69

<210> 18
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR primer

<400> 18
cctcttttgc cttctacttg a 21

<210> 19
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR primer

<400> 19
gcgctcgagt tacactgccc gtgccaggc 29

<210> 20
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR primer

<400> 20
tgggtaacat caccattgga a 21

<210> 21
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR primer

<400> 21
tttctgagcc tgtttttgcc 20

<210> 22
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR primer

<400> 22
tgggtaacat caccattgga ac 22

<210> 23
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:PCR primer

<400> 23
caaacatcac cacactgccc tcc 23

<210> 24
<211> 380
<212> PRT
<213> bovidae

<400> 24
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Leu Lys Thr Met Arg Asn Val Val Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu His Ala Tyr Ser Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr His Pro Leu Arg
50 55 60

Asn Ile Lys Asp Leu Val Tyr Met Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Ala Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Asp Phe Cys Thr Ser Pro Ala Cys Ser Thr His Val Arg
100 105 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Leu Thr Asn Lys Thr Phe
115 120 125

Arg Ile Thr Tyr Gly Ser Gly Arg Met Lys Gly Val Val Val His Asp
130 135 140

Thr Val Arg Ile Gly Asn Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Ile Glu Glu Tyr Gly Phe Glu Gly Arg Ile Tyr Asp Gly Val Leu
165 170 175

Gly Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Gln Arg Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Glu Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Glu Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Gln Ala Gly Asp Trp Ser Val His Met Asp Arg Ile Ser Ile Glu Arg
245 250 255

Lys Ile Ile Ala Cys Ser Asp Gly Cys Lys Ala Leu Val Asp Thr Gly
260 265 270

Thr Ser Asp Ile Val Gly Pro Arg Arg Leu Val Asn Asn Ile His Arg
275 280 285

Leu Ile Gly Ala Ile Pro Arg Gly Ser Glu His Tyr Val Pro Cys Ser
290 295 300

Glu Val Asn Thr Leu Pro Ser Ile Val Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Gly Arg Ala Tyr Ile Leu Lys Asp Asp Arg Gly Arg
325 330 335

Cys Tyr Thr Thr Phe Gln Glu Asn Arg Val Ser Ser Ser Thr Glu Thr
340 345 350

Trp Tyr Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 25
<211> 376
<212> PRT
<213> bovidae

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Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Leu Ser Glu Cys Ile
1 5 10 15

Val Ile Leu Pro Leu Lys Lys Met Lys Thr Leu Arg Glu Thr Leu Arg
20 25 30

Glu Lys Asn Leu Leu Asn Asn Phe Leu Glu Glu Gln Ala Tyr Arg Leu
35 40 45

Ser Lys Asn Asp Ser Lys Ile Thr Ile His Pro Leu Arg Asn Tyr Leu
50 55 60

Asp Thr Ala Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro Pro Gln Glu
65 70 75 80

Phe Arg Val Val Phe Asp Thr Gly Ser Ala Asn Leu Trp Val Pro Cys
85 90 95

```
Ile Thr Cys Thr Ser Pro Ala Cys Tyr Thr His Lys Thr Phe Asn Pro
            100                 105                 110

Gln Asn Ser Ser Ser Phe Arg Glu Val Gly Ser Pro Ile Thr Ile Phe
        115                 120                 125

Tyr Gly Ser Gly Ile Ile Gln Gly Phe Leu Gly Ser Asp Thr Val Arg
    130                 135                 140

Ile Gly Asn Leu Val Ser Pro Glu Gln Ser Phe Gly Leu Ser Leu Glu
145                 150                 155                 160

Glu Tyr Gly Phe Asp Ser Leu Pro Phe Asp Gly Ile Leu Gly Leu Ala
                165                 170                 175

Phe Pro Ala Met Gly Ile Glu Asp Thr Ile Pro Ile Phe Asp Asn Leu
            180                 185                 190

Trp Ser His Gly Ala Phe Ser Glu Pro Val Phe Ala Phe Tyr Leu Asn
        195                 200                 205

Thr Asn Lys Pro Glu Gly Ser Val Val Met Phe Gly Gly Val Asp His
    210                 215                 220

Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Val Ser Gln Thr Ser
225                 230                 235                 240

His Trp Gln Ile Ser Met Asn Asn Ile Ser Met Asn Gly Thr Val Thr
                245                 250                 255

Ala Cys Ser Cys Gly Cys Glu Ala Leu Leu Asp Thr Gly Thr Ser Met
            260                 265                 270

Ile Tyr Gly Pro Thr Lys Leu Val Thr Asn Ile His Lys Leu Met Asn
        275                 280                 285

Ala Arg Leu Glu Asn Ser Glu Tyr Val Val Ser Cys Asp Ala Val Lys
    290                 295                 300

Thr Leu Pro Pro Val Ile Phe Asn Ile Asn Gly Ile Asp Tyr Pro Leu
305                 310                 315                 320

Arg Pro Gln Ala Tyr Ile Ile Lys Ile Gln Asn Ser Cys Arg Ser Val
                325                 330                 335

Phe Gln Gly Gly Thr Glu Asn Ser Ser Leu Asn Thr Trp Ile Leu Gly
            340                 345                 350

Asp Ile Phe Leu Arg Gln Tyr Phe Ser Val Phe Asp Arg Lys Asn Arg
        355                 360                 365

Arg Ile Gly Leu Ala Pro Ala Val
    370                 375
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<210> 26
<211> 381
<212> PRT
<213> bovidae

<400> 26

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Met Asp Asp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
 1               5                  10                  15

Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Arg Asn Thr Val Ser
            20                  25                  30

Gly Lys Asn Ile Leu Asn Asn Ile Leu Lys Glu His Val Tyr Arg Leu
        35                  40                  45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr His Pro Leu Arg
    50                  55                  60

Asn Ile Lys Asp Leu Ile Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65                  70                  75                  80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Phe Trp
                85                  90                  95

Val Pro Ser Asp Phe Cys Thr Ser Arg Ala Cys Ser Thr His Val Arg
            100                 105                 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Leu Thr Asn Lys Thr Phe
        115                 120                 125

Arg Ile Thr Tyr Gly Ser Gly Arg Met Lys Gly Val Val Ala His Asp
    130                 135                 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145                 150                 155                 160

Ser Val Glu Glu Tyr Gly Phe Glu Gly Arg Ala Tyr Tyr Asp Gly Val
                165                 170                 175

Leu Gly Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile
            180                 185                 190

Phe Asp Asn Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala
        195                 200                 205

Ile Leu Leu Ser Lys Asp Glu Gln Glu Gly Ser Val Val Met Phe Gly
    210                 215                 220

Gly Val Asp His Arg Tyr Tyr Glu Gly Glu Leu Asn Trp Val Pro Leu
225                 230                 235                 240

Ile Glu Ala Gly Asp Trp Ile Ile His Met Asp Arg Ile Ser Met Lys
                245                 250                 255
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Arg Lys Ile Ile Ala Cys Ser Gly Ser Cys Glu Ala Ile Val Asp Thr
260 265 270

Gly Thr Ser Ala Ile Glu Gly Pro Arg Lys Leu Val Asn Lys Ile His
275 280 285

Lys Leu Ile Gly Ala Arg Pro Arg His Ser Lys Tyr Tyr Ile Ser Cys
290 295 300

Ser Ala Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile
305 310 315 320

Asn Tyr Pro Cys Pro Gly Arg Ala Tyr Val Leu Lys Asp Ser Arg Gly
325 330 335

Arg Cys Tyr Ser Met Phe Gln Glu Asn Lys Val Ser Ser Ser Thr Glu
340 345 350

Thr Trp Ile Leu Gly Asp Val Phe Leu Arg Val Tyr Phe Ser Val Phe
355 360 365

Asp Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 27
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Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Thr Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Val Lys Glu His Ala Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Arg Asp Phe Phe Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Glu Leu Trp
85 90 95

Val Pro Ser Ile Phe Cys Asn Ser Ser Thr Cys Ser Lys His Asp Arg
100 105 110

Phe Arg His Leu Glu Ser Ser Thr Phe Arg Leu Ser Arg Arg Thr Phe
115 120 125

Ser Ile Thr Tyr Gly Ser Gly Arg Ile Glu Ala Leu Val Val His Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Gln Phe Gly Leu
145 150 155 160

Cys Leu Glu Glu Ser Gly Phe Glu Gly Met Arg Phe Asp Gly Val Leu
165 170 175

Gly Leu Ser Tyr Thr Asn Ile Ser Pro Ser Gly Ala Ile Pro Ile Phe
180 185 190

Tyr Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Glu Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Ala Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Leu Met
225 230 235 240

Lys Ala Gly Asp Trp Ser Val His Met Asp Arg Ile Ser Met Lys Arg
245 250 255

Lys Val Ile Ala Cys Ser Gly Gly Cys Lys Ala Leu Val Asp Thr Gly
260 265 270

Ser Ser Asp Ile Val Gly Pro Ser Thr Leu Val Asn Asn Ile Trp Lys
275 280 285

Leu Ile Gly Ala Thr Pro Gln Gly Ser Glu His Tyr Val Ser Cys Ser
290 295 300

Ala Val Asn Ser Leu Pro Ser Ile Ile Phe Thr Ile Lys Ser Asn Asn
305 310 315 320

Tyr Arg Val Pro Gly Gln Ala Tyr Ile Leu Lys Asp Ser Arg Gly Arg
325 330 335

Cys Phe Thr Ala Phe Lys Gly His Gln Gln Ser Ser Ser Thr Glu Met
340 345 350

Trp Ile Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Arg Lys Asp Arg Ile Gly Leu Ala Thr Lys Val
370 375 380

<210> 28
<211> 377
<212> PRT
<213> bovidae

<400> 28

Met Lys Trp Leu Val Leu Leu Gly Leu Leu Thr Ser Ser Glu Cys Ile
1   5   10   15

Val Ile Leu Pro Leu Thr Lys Val Lys Thr Met Arg Lys Thr Leu Ser
            20   25   30

Glu Lys Asn Met Leu Asn Asn Phe Leu Lys Glu Gln Ala Tyr Arg Leu
        35   40   45

Ser Gln Ile Ser Ser Arg Gly Ser Asn Ile Thr Ile His Pro Leu Arg
    50   55   60

Asn Ile Met Asp Met Val Tyr Val Gly Lys Ile Thr Ile Gly Thr Pro
65   70   75   80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Glu Leu Trp
                85   90   95

Val Pro Ser Val Phe Cys Pro Ser Ser Ala Cys Ser Thr His Ile Arg
            100   105   110

Phe Arg His Leu Glu Ser Ser Thr Ser Gly Leu Thr Gln Lys Thr Phe
        115   120   125

Ser Ile Thr Tyr Gly Ser Gly Ser Thr Lys Gly Phe Leu Ala Tyr Asp
    130   135   140

Thr Val Arg Ile Gly Asp Leu Leu Ser Thr Asp Gln Glu Phe Gly Leu
145   150   155   160

Ser Met Glu Glu His Gly Phe Glu Asp Leu Pro Phe Asp Gly Val Leu
                165   170   175

Gly Leu Asn Tyr Pro Asp Met Ser Phe Ile Thr Thr Ile Pro Ile Phe
            180   185   190

Asp Asn Leu Lys Asn Gln Gly Ala Phe Ser Glu Pro Val Phe Ala Phe
        195   200   205

Tyr Leu Gly Lys Val Lys Gly Ser Val Val Met Phe Gly Gly Val Asp
    210   215   220

His Thr Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile Gln Ala
225   230   235   240

Gly Glu Trp Ser Leu His Met Asp Arg Ile Ser Met Lys Arg Lys Val
                245   250   255

Ile Ala Cys Ser Gly Gly Cys Glu Ala Phe Tyr Asp Thr Gly Thr Ser
            260   265   270

Leu Ile Leu Gly Pro Arg Arg Leu Val Asn Asn Ile Gln Lys Leu Ile
        275   280   285

Gly Ala Thr Pro Gln Gly Ser Glu His Tyr Ile Ser Cys Phe Ala Val
290 295 300

Ile Ser Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn Ile Pro
305 310 315 320

Val Pro Ala Arg Ala Tyr Ile His Lys Asp Ser Arg Gly His Cys Tyr
325 330 335

Pro Thr Phe Lys Glu Asn Thr Val Ser Thr Ser Thr Glu Thr Trp Ile
340 345 350

Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp Arg Gly
355 360 365

Asn Asp Arg Ile Gly Leu Ala Gln Val
370 375

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20 25 30

Gly Lys Asn Thr Leu Asn Asn Ile Leu Lys Glu His Ala Tyr Arg Leu
35 40 45

Pro Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr His Pro Leu Arg Asn
50 55 60

Ile Arg Asp Leu Phe Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro Pro
65 70 75 80

Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Asp Leu Trp Val
85 90 95

Ala Ser Ile Phe Cys Asn Ser Ser Ser Cys Ala Ala His Val Arg Phe
100 105 110

Arg His His Gln Ser Ser Thr Phe Arg Pro Thr Asn Lys Thr Phe Arg
115 120 125

Ile Thr Tyr Gly Ser Gly Arg Met Lys Gly Val Val Val His Asp Thr
130 135 140

Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu Cys
145 150 155 160

Leu Lys Asp Ser Gly Phe Lys Gly Ile Pro Phe Asp Gly Ile Leu Gly
165 170 175

Leu Ser Tyr Pro Asn Lys Thr Phe Ser Gly Ala Phe Pro Ile Phe Asp
180 185 190

Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe Tyr
195 200 205

Leu Ser Lys Asp Lys Gln Glu Gly Ser Val Val Met Phe Gly Gly Val
210 215 220

Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile Gln
225 230 235 240

Val Gly Asp Trp Phe Val His Met Asp Arg Thr Thr Met Lys Arg Lys
245 250 255

Val Ile Ala Cys Ser Asp Gly Cys Lys Ala Leu Val Asp Thr Gly Thr
260 265 270

Ser Asp Ile Val Gly Pro Ser Thr Leu Val Asn Asn Ile Trp Lys Leu
275 280 285

Ile Arg Ala Arg Pro Leu Gly Pro Gln Tyr Phe Val Ser Cys Ser Ala
290 295 300

Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn Tyr
305 310 315 320

Arg Leu Pro Ala Arg Ala Tyr Ile His Lys Asp Ser Arg Gly Arg Cys
325 330 335

Tyr Thr Ala Phe Lys Glu His Arg Phe Ser Ser Pro Ile Glu Thr Trp
340 345 350

Leu Leu Gly Asp Val Phe Leu Arg Arg Tyr Phe Ser Val Phe Asp Arg
355 360 365

Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375

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20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu Asp Pro Tyr Arg Leu
35 40 45

Ser His Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Arg Asp Ile Phe Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Ile Asp Cys Asn Ser Thr Ser Cys Ala Thr His Val Arg
100 105 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Pro Thr Asn Lys Thr Phe
115 120 125

Arg Ile Ile Tyr Gly Ser Gly Arg Met Asn Gly Val Ile Ala Tyr Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Val Glu Glu Tyr Gly Phe Ala His Lys Arg Phe Asp Gly Ile Leu
165 170 175

Gly Leu Asn Tyr Trp Asn Leu Ser Trp Ser Lys Ala Met Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Asn Ile Thr Met Asn Arg Glu Val Ile Ala Cys Ser Glu
210 215 220

Gly Cys Ala Ala Leu Val Asp Thr Gly Ser Ser Asn Ile Gln Gly Pro
225 230 235 240

Gly Arg Leu Ile Asp Asn Ile Gln Arg Ile Ile Gly Ala Thr Pro Arg
245 250 255

Gly Ser Lys Tyr Tyr Val Ser Cys Ser Ala Val Asn Ile Leu Pro Ser
260 265 270

Ile Ile Phe Thr Ile Asn Gly Val Asn Tyr Pro Val Pro Pro Arg Ala
275 280 285

Tyr Ile Leu Lys Asp Ser Arg Gly His Cys Tyr Thr Thr Phe Lys Glu
290 295 300

Lys Arg Val Arg Arg Ser Thr Glu Ser Trp Val Leu Gly Glu Val Phe
305 310 315 320

Leu Arg Leu Tyr Phe Ser Val Phe Asp Arg Gly Asn Asp Arg Ile Gly
                325   330   335

Leu Ala Arg Arg Val
            340

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<400> 31
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Val Lys Ile Pro Leu Thr Lys Met Lys Thr Met Gln Glu Ala Ile Arg
            20   25   30

Glu Lys Gln Leu Leu Glu Asp Phe Leu Asp Glu Gln Pro His Ser Leu
        35   40   45

Ser Gln His Ser Asp Pro Asp Lys Lys Phe Ser Ser His Gln Leu Lys
    50   55   60

Asn Phe Gln Asn Ala Val Tyr Phe Gly Thr Ile Thr Ile Gly Thr Pro
65   70   75   80

Pro Gln Glu Phe Gln Val Asn Phe Asp Thr Gly Ser Ser Asp Leu Trp
                85   90   95

Val Pro Ser Val Asp Cys Gln Ser Pro Ser Cys Ser Lys His Lys Arg
            100   105   110

Phe Asp Pro Gln Lys Ser Thr Thr Phe Gln Pro Leu Asn Gln Lys Ile
        115   120   125

Glu Leu Val Tyr Gly Ser Gly Thr Met Lys Gly Val Leu Gly Ser Asp
    130   135   140

Thr Ile Gln Ile Gly Asn Leu Val Ile Val Asn Gln Ile Phe Gly Leu
145   150   155   160

Ser Gln Asn Gln Ser Ser Gly Val Leu Glu Gln Val Pro Tyr Asp Gly
                165   170   175

Ile Leu Gly Leu Ala Tyr Pro Ser Leu Ala Ile Gln Gly Thr Thr Pro
            180   185   190

Val Phe Asp Asn Leu Lys Asn Arg Glu Val Ile Ser Glu Pro Val Phe
        195   200   205

Ala Phe Tyr Leu Ser Ser Arg Pro Glu Asn Ile Ser Thr Val Met Phe
    210   215   220

Gly Gly Val Asp His Thr Tyr His Lys Gly Lys Leu Gln Trp Ile Pro
225 230 235 240

Val Thr Gln Ala Arg Phe Trp Gln Val Ala Met Ser Ser Met Thr Met
245 250 255

Asn Gly Asn Val Val Gly Cys Ser Gln Gly Cys Gln Ala Val Val Asp
260 265 270

Thr Gly Thr Ser Leu Leu Val Gly Pro Thr His Leu Val Thr Asp Ile
275 280 285

Leu Lys Leu Ile Asn Pro Asn Pro Ile Leu Asn Asp Glu Gln Met Leu
290 295 300

Ser Cys Asp Ala Ile Asn Ser Leu Pro Thr Leu Leu Leu Thr Ile Asn
305 310 315 320

Gly Ile Val Tyr Pro Val Pro Pro Asp Tyr Tyr Ile Gln Arg Phe Ser
325 330 335

Glu Arg Ile Cys Phe Ile Ser Phe Gln Gly Gly Thr Glu Ile Leu Lys
340 345 350

Asn Leu Gly Thr Ser Glu Thr Trp Ile Leu Gly Asp Val Phe Leu Arg
355 360 365

Leu Tyr Phe Ser Val Tyr Asp Arg Gly Asn Asn Arg Ile Gly Leu Ala
370 375 380

Pro Ala Ala
385

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<211> 379
<212> PRT
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<400> 32
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Val Lys Ile Pro Leu Arg Gln Val Lys Thr Met Arg Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Lys Asn Phe Leu Lys Glu His Pro Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Met Asn Leu Val Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Phe Cys Thr Met Pro Ala Cys Ser Ala Pro Val Trp Phe
100 105 110

Arg Gln Leu Gln Ser Ser Thr Phe Gln Pro Thr Asn Lys Thr Phe Thr
115 120 125

Ile Thr Tyr Gly Ser Gly Ser Met Lys Gly Phe Leu Ala Tyr Asp Thr
130 135 140

Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu Ser
145 150 155 160

Val Val Glu Tyr Gly Leu Glu Gly Arg Asn Tyr Asp Gly Val Leu Gly
165 170 175

Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile Phe Asp
180 185 190

Asn Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe Tyr
195 200 205

Leu Ser Lys Asn Lys Gln Glu Gly Ser Val Val Met Phe Gly Gly Val
210 215 220

Asp His Gln Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Leu Ile Glu
225 230 235 240

Ala Gly Glu Trp Arg Val His Met Asp Arg Ile Ser Met Lys Arg Thr
245 250 255

Val Ile Ala Cys Ser Asp Gly Cys Glu Ala Leu Val His Thr Gly Thr
260 265 270

Ser His Ile Glu Gly Pro Gly Arg Leu Val Asn Asn Ile His Arg Leu
275 280 285

Ile Arg Thr Arg Pro Phe Asp Ser Lys His Tyr Val Ser Cys Phe Ala
290 295 300

Thr Lys Tyr Leu Pro Ser Ile Thr Phe Ile Ile Asn Gly Ile Lys Tyr
305 310 315 320

Pro Met Thr Ala Arg Ala Tyr Ile Phe Lys Asp Ser Arg Gly Arg Cys
325 330 335

Tyr Ser Ala Phe Lys Glu Asn Thr Val Arg Thr Ser Arg Glu Thr Trp
340 345 350

Ile Leu Gly Asp Ala Phe Leu Arg Arg Tyr Phe Ser Val Phe Asp Arg
355 360 365

Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375

<210> 33
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Val Ile Ile Pro Leu Arg Gln Met Lys Thr Met Arg Glu Thr Leu Arg
20 25 30

Glu Arg His Leu Leu Thr Asn Phe Ser Glu Glu His Pro Tyr Asn Leu
35 40 45

Ser Gln Lys Ala Ala Asn Asp Gln Asn Ile Ile Tyr His His Pro Leu
50 55 60

Arg Ser Tyr Lys Asp Phe Ser Tyr Ile Gly Asn Ile Asn Ile Gly Thr
65 70 75 80

Pro Pro Gln Glu Phe Gln Val Leu Phe Asp Thr Gly Ser Ser Ser Leu
85 90 95

Trp Val Pro Ser Ile Tyr Cys Gln Ser Ser Ser Cys Tyr Lys His Asn
100 105 110

Ser Phe Val Pro Cys Asn Ser Ser Thr Phe Lys Ala Thr Asn Lys Ile
115 120 125

Phe Asn Thr Asn Tyr Thr Ala Thr Ser Ile Lys Gly Tyr Leu Val Tyr
130 135 140

Asp Thr Val Arg Ile Gly Asn Leu Val Ser Val Ala Gln Pro Phe Gly
145 150 155 160

Leu Ser Leu Lys Glu Phe Gly Phe Asp Asp Val Pro Phe Asp Gly Ile
165 170 175

Leu Gly Leu Gly Tyr Pro Arg Arg Thr Ile Thr Gly Ala Asn Pro Ile
180 185 190

Phe Asp Asn Leu Trp Lys Gln Gly Val Ile Ser Glu Pro Val Phe Ala
195 200 205

Phe Tyr Leu Ser Ser Gln Lys Glu Asn Gly Ser Val Val Met Phe Gly
210 215 220

Gly Val Asn Arg Ala Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Val
225 230 235 240

Ser Gln Val Gly Ser Trp His Ile Asn Ile Asp Ser Ile Ser Met Asn
                245   250   255

Gly Thr Val Val Ala Cys Lys Arg Gly Cys Gln Ala Ser Trp Ile Arg
            260   265   270

Gly Arg Leu Ser Ala Trp Pro Lys Arg Ile Val Ser Lys Ile Gln Lys
        275   280   285

Leu Ile His Ala Arg Pro Ile Asp Arg Glu His Val Val Ser Cys Gln
    290   295   300

Ala Ile Gly Thr Leu Pro Pro Ala Val Phe Thr Ile Asn Gly Ile Asp
305   310   315   320

Tyr Pro Val Pro Ala Gln Ala Tyr Ile Gln Ser Leu Ser Gly Tyr Cys
                325   330   335

Phe Ser Asn Phe Leu Val Arg Pro Gln Arg Val Asn Glu Ser Glu Thr
            340   345   350

Trp Ile Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
        355   360   365

Arg Gly Asn Asn Arg Ile Gly Leu Ala Pro Ala Val
    370   375   380

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<400> 34
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  1   5   10   15

Val Ile Met Leu Leu Thr Lys Thr Lys Thr Met Arg Glu Ile Trp Arg
            20   25   30

Glu Lys Lys Leu Leu Asn Ser Phe Leu Glu Glu Gln Ala Asn Arg Met
        35   40   45

Ser Asp Asp Ser Ala Ser Asp Pro Lys Leu Ser Thr His Pro Leu Arg
    50   55   60

Asn Ala Leu Asp Met Ala Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
 65   70   75   80

Pro Lys Glu Phe Arg Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
                85   90   95

Val Pro Ser Ile Lys Cys Ile Ser Pro Ala Cys His Thr His Ile Thr
            100   105   110

Phe Asp His His Lys Ser Ser Thr Phe Arg Leu Thr Arg Arg Pro Phe
115 120 125

His Ile Leu Tyr Gly Ser Gly Met Met Asn Gly Val Leu Ala Tyr Asp
130 135 140

Thr Val Arg Ile Gly Lys Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Leu Gln Gln Phe Gly Phe Asp Asn Ala Pro Phe Asp Gly Val Leu
165 170 175

Gly Leu Ser Tyr Pro Ser Leu Ala Val Pro Gly Thr Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Gln Gln Gly Ala Ile Ser Glu Pro Ile Phe Ala Phe
195 200 205

Tyr Leu Ser Thr Arg Lys Glu Asn Gly Ser Val Leu Met Leu Gly Gly
210 215 220

Val Asp His Ser Tyr His Lys Gly Lys Leu Asn Trp Ile Pro Val Ser
225 230 235 240

Gln Thr Lys Ser Trp Leu Ile Thr Val Asp Arg Ile Ser Met Asn Gly
245 250 255

Arg Val Ile Gly Cys Glu His Gly Cys Glu Ala Leu Val Asp Thr Gly
260 265 270

Thr Ser Leu Ile His Gly Pro Ala Arg Pro Val Thr Asn Ile Gln Lys
275 280 285

Phe Ile His Ala Met Pro Tyr Gly Ser Glu Tyr Met Val Leu Cys Pro
290 295 300

Val Ile Ser Ile Leu Pro Pro Val Ile Phe Thr Ile Asn Gly Ile Asp
305 310 315 320

Tyr Ser Val Pro Arg Glu Ala Tyr Ile Gln Lys Ile Ser Asn Ser Leu
325 330 335

Cys Leu Ser Thr Phe His Gly Asp Asp Thr Asp Gln Trp Ile Leu Gly
340 345 350

Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Tyr Asp Arg Gly Asn Asn
355 360 365

Arg Ile Gly Leu Ala Pro Ala Val
370 375

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Val Ile Leu Pro Leu Arg Lys Met Lys Thr Leu Arg Glu Thr Leu Arg
20 25 30

Glu Lys Asn Leu Leu Asn Asn Phe Leu Glu Glu Arg Ala Tyr Arg Leu
35 40 45

Ser Lys Lys Asp Ser Lys Ile Thr Ile His Pro Leu Lys Asn Tyr Leu
50 55 60

Asp Met Ala Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro Pro Gln Glu
65 70 75 80

Phe Arg Val Val Phe Asp Thr Gly Ser Ala Asp Leu Trp Val Pro Ser
85 90 95

Ile Ser Cys Val Ser Pro Ala Cys Tyr Thr His Lys Thr Phe Asn Leu
100 105 110

His Asn Ser Ser Ser Phe Gly Gln Thr His Gln Pro Ile Ser Ile Ser
115 120 125

Tyr Gly Pro Gly Ile Ile Gln Gly Phe Leu Gly Ser Asp Thr Val Arg
130 135 140

Ile Gly Asn Leu Val Ser Leu Lys Gln Ser Phe Gly Leu Ser Gln Glu
145 150 155 160

Glu Tyr Gly Phe Asp Gly Ala Pro Phe Asp Gly Val Leu Gly Leu Ala
165 170 175

Tyr Pro Ser Ile Ser Ile Lys Gly Ile Ile Pro Ile Phe Asp Asn Leu
180 185 190

Trp Ser Gln Gly Ala Phe Ser Glu Pro Val Phe Ala Phe Tyr Leu Asn
195 200 205

Thr Cys Gln Pro Glu Gly Ser Val Val Met Phe Gly Gly Val Asp His
210 215 220

Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Val Ser Gln Thr Arg
225 230 235 240

Tyr Trp Gln Ile Ser Met Asn Arg Ile Ser Met Asn Gly Asn Val Thr
245 250 255

Ala Cys Ser Arg Gly Cys Gln Ala Leu Leu Asp Thr Gly Thr Ser Met
260 265 270

Ile His Gly Pro Thr Arg Leu Ile Thr Asn Ile His Lys Leu Met Asn
275 280 285

Ala Arg His Gln Gly Ser Glu Tyr Val Val Ser Cys Asp Ala Val Lys
290 295 300

Thr Leu Pro Pro Val Ile Phe Asn Ile Asn Gly Ile Asp Tyr Pro Leu
305 310 315 320

Pro Pro Gln Ala Tyr Ile Thr Lys Ala Gln Asn Phe Cys Leu Ser Ile
325 330 335

Phe His Gly Gly Thr Glu Thr Ser Ser Pro Glu Thr Trp Ile Leu Gly
340 345 350

Gly Val Phe Leu Arg Gln Tyr Phe Ser Val Phe Asp Arg Arg Asn Asp
355 360 365

Ser Ile Gly Leu Ala Gln Val
370 375

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Glu Lys Asn Leu Leu Asn Asn Phe Leu Glu Glu Gln Ala Tyr Arg Leu
35 40 45

Ser Lys Asn Asp Ser Lys Ile Thr Ile His Pro Leu Arg Asn Tyr Leu
50 55 60

Asp Thr Ala Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro Pro Gln Glu
65 70 75 80

Phe Arg Val Val Phe Asp Thr Gly Ser Ala Asn Leu Trp Val Pro Cys
85 90 95

Ile Thr Cys Thr Ser Pro Ala Cys Tyr Thr His Lys Thr Phe Asn Pro
100 105 110

Gln Asn Ser Ser Ser Phe Arg Glu Val Gly Ser Pro Ile Thr Ile Phe
115 120 125

Tyr Gly Ser Gly Ile Ile Gln Gly Phe Leu Gly Ser Asp Thr Val Arg
130 135 140

Ile Gly Asn Leu Val Ser Leu Lys Gln Ser Phe Gly Leu Ser Gln Glu
145 150 155 160

Glu Tyr Gly Phe Asp Gly Ala Pro Phe Asp Gly Val Leu Gly Leu Ala
165 170 175

Tyr Pro Ser Ile Ser Ile Lys Gly Ile Ile Pro Ile Phe Asp Asn Leu
180 185 190

Trp Ser His Gly Ala Phe Ser Glu Pro Val Phe Ala Phe Tyr Leu Asn
195 200 205

Thr Asn Lys Pro Glu Gly Ser Val Val Met Phe Gly Gly Val Asp His
210 215 220

Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Val Ser Gln Thr Ser
225 230 235 240

His Trp Gln Ile Ser Met Asn Asn Ile Ser Met Asn Gly Thr Val Thr
245 250 255

Ala Cys Ser Cys Gly Cys Glu Ala Leu Leu Asp Thr Gly Thr Ser Met
260 265 270

Ile Tyr Gly Pro Thr Lys Leu Val Thr Asn Ile His Lys Leu Met Asn
275 280 285

Ala Arg Leu Glu Asn Ser Glu Tyr Val Val Ser Cys Asp Ala Val Lys
290 295 300

Thr Leu Pro Pro Val Ile Phe Asn Ile Asn Gly Ile Asp Tyr Pro Leu
305 310 315 320

Arg Pro Gln Ala Tyr Ile Ile Lys Ile Gln Asn Asn Cys Arg Ser Val
325 330 335

Phe Gln Gly Gly Thr Glu Asn Ser Ser Leu Asn Thr Trp Ile Leu Gly
340 345 350

Asp Ile Phe Leu Arg Gln Tyr Phe Ser Val Phe Asp Arg Lys Asn Arg
355 360 365

Arg Ile Cys Trp His Arg Trp Val Pro Thr Thr Arg Thr Thr Met Thr
370 375 380

Ser Lys Leu Pro Pro Lys Leu
385 390

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35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr His Pro Leu Met
50 55 60

Asn Ile Trp Asp Leu Leu Tyr Leu Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Leu Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Leu Leu Cys Asn Ser Ser Thr Cys Ala Lys His Val Met
100 105 110

Phe Arg His Arg Leu Ser Ser Thr Tyr Arg Pro Thr Asn Lys Thr Phe
115 120 125

Met Ile Phe Tyr Ala Val Gly Lys Ile Glu Gly Val Val Val Arg Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Ala Asp Gln Thr Phe Gly Leu
145 150 155 160

Ser Ile Ala Glu Thr Gly Phe Glu Asn Thr Thr Leu Asp Gly Ile Leu
165 170 175

Gly Leu Ser Tyr Pro Asn Thr Ser Cys Phe Gly Thr Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Leu His Ser
195 200 205

Val Arg Arg Lys Asp Glu Gln Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Ser Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Lys Ala Gly Asp Trp Ser Val Arg Val Asp Ser Ile Thr Met Lys Arg
245 250 255

Glu Val Ile Ala Cys Ser Asp Gly Cys Arg Ala Leu Val Asp Thr Gly
260 265 270

Ser Ser His Ile Gln Gly Pro Gly Arg Leu Ile Asp Asn Val Gln Lys
275 280 285

Leu Ile Gly Thr Met Pro Gln Gly Ser Met His Tyr Val Pro Cys Ser
290 295 300

Ala Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Ser Ile Ser
305 310 315 320

Tyr Thr Val Pro Ala Gln Ala Tyr Ile Leu Lys Gly Ser Arg Gly Arg
325 330 335

Cys Tyr Ser Thr Phe Gln Gly His Thr Met Ser Ser Ser Thr Glu Thr
340 345 350

Trp Ile Leu Gly Asp Val Phe Leu Ser Gln Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Gln Val Gly Thr Asp Tyr Lys
370 375 380

Asp Asp Asp Glu Ser Pro Lys Leu
385 390

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20 25 30

Glu Lys Asp Arg Leu Lys Asp Phe Leu Glu Asn His Pro Tyr Asn Leu
35 40 45

Ala Tyr Lys Phe Val Asp Ser Val Asn Leu Asp Leu Gly Ile Tyr Phe
50 55 60

Glu Pro Met Arg Asn Tyr Leu Asp Leu Ala Tyr Val Gly Thr Ile Ser
65 70 75 80

Ile Gly Thr Pro Pro Gln Glu Phe Lys Val Ile Phe Asp Thr Gly Ser
85 90 95

Ser Asp Leu Trp Val Pro Ser Ile Tyr Cys Ser Ser Pro Ala Cys Ala
100 105 110

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Asn His Asn Val Phe Asn Pro Leu Arg Ser Ser Thr Phe Arg Ile Ser
        115                 120                 125

Gly Arg Pro Ile His Leu Gln Tyr Gly Ser Gly Thr Met Ser Gly Phe
    130                 135                 140

Leu Ala Tyr Asp Thr Val Arg Phe Gly Gly Leu Val Asp Val Ala Gln
145                 150                 155                 160

Ala Phe Gly Leu Ser Leu Arg Glu Pro Gly Lys Phe Met Glu Tyr Ala
                165                 170                 175

Val Phe Asp Gly Ile Leu Gly Leu Ala Tyr Pro Ser Leu Ser Leu Arg
            180                 185                 190

Gly Thr Val Pro Val Phe Asp Asn Leu Trp Lys Gln Gly Leu Ile Ser
        195                 200                 205

Gln Glu Leu Phe Ala Phe Tyr Leu Ser Lys Lys Asp Glu Glu Gly Ser
    210                 215                 220

Val Val Met Phe Gly Gly Val Asp His Ser Tyr Tyr Ser Gly Asp Leu
225                 230                 235                 240

Asn Trp Val Pro Val Ser Lys Arg Leu Tyr Trp Gln Leu Ser Met Asp
                245                 250                 255

Ser Ile Ser Met Asn Gly Glu Val Ile Ala Cys Asp Gly Gly Cys Gln
            260                 265                 270

Ala Ile Ile Asp Thr Gly Thr Ser Leu Leu Ile Gly Pro Ser His Val
        275                 280                 285

Val Phe Asn Ile Gln Met Ile Ile Gly Ala Asn Gln Ser Tyr Ser Gly
    290                 295                 300

Glu Tyr Val Val Asp Cys Asp Ala Ala Asn Thr Leu Pro Asp Ile Val
305                 310                 315                 320

Phe Thr Ile Asn Gly Ile Asp Tyr Pro Val Pro Ala Ser Ala Tyr Ile
                325                 330                 335

Gln Glu Gly Pro Gln Gly Thr Cys Tyr Ser Gly Phe Asp Glu Ser Gly
            340                 345                 350

Asp Ser Leu Leu Val Ser Asp Ser Trp Ile Leu Gly Asp Val Phe Leu
        355                 360                 365

Arg Leu Tyr Phe Thr Val Phe Asp Arg Glu Asn Asn Arg Ile Gly Leu
    370                 375                 380

Ala Leu Ala Val
385
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tgccctcgat cgattgcaac agtacatcct gtgctacaca tgttaggttc agacatcttc 360
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acggcgtcaa ctacccagtg ccacctcgag cttacatcct caaggattct agaggccact 1020
gctataccac ctttaaagag aaaagagtga ggagatctac agagagctgg gtcctgggtg 1080
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cacgggcagt gtaactcg 1158

<210> 40
<211> 380
<212> PRT
<213> bovidae

<400> 40
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Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Arg Lys Thr Leu Ser
            20   25   30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu Asp Pro Tyr Arg Leu
        35   40   45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
    50   55   60

Asn Ile Arg Asp Ile Phe Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65   70   75   80

Pro Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Asp Leu Trp
                85   90   95

Val Pro Ser Ile Asp Cys Asn Ser Thr Ser Cys Ala Thr His Val Arg
            100   105   110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Pro Thr Asn Lys Thr Phe
115 120 125

Arg Ile Ile Tyr Gly Ser Gly Arg Met Asn Gly Val Ile Ala Tyr Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Val Glu Glu Tyr Gly Phe Ala His Lys Arg Phe Asp Gly Ile Leu
165 170 175

Gly Leu Asn Tyr Trp Asn Leu Ser Trp Ser Lys Ala Met Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Lys Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Lys Trp Val Pro Leu Ile
225 230 235 240

Gln Ala Val Asp Trp Ser Val His Val Asp Arg Ile Thr Met Asn Arg
245 250 255

Glu Val Ile Ala Cys Ser Glu Gly Cys Ala Ala Leu Val Asp Thr Gly
260 265 270

Ser Ser Asn Ile Gln Gly Pro Arg Arg Leu Ile Asp Asn Ile Gln Arg
275 280 285

Ile Ile Gly Ala Thr Pro Arg Gly Ser Lys Tyr Tyr Val Ser Cys Ser
290 295 300

Ala Val Asn Ile Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Val Asn
305 310 315 320

Tyr Pro Val Pro Pro Arg Ala Tyr Ile Leu Lys Asp Ser Arg Gly His
325 330 335

Cys Tyr Thr Thr Phe Lys Glu Lys Arg Val Arg Arg Ser Thr Glu Ser
340 345 350

Trp Val Leu Gly Glu Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 41
<211> 1155
<212> DNA
<213> bovidae

<400> 41
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tgaagaattt cttgaaggag catccttaca gactgtccca gatttctttt cgtggctcaa 180
atctaactat tcacccgctg aggaacatca tgaatttggt ctacgtgggt aacatcacca 240
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tgccctcctt ttgtaccatg ccagcatgct ctgcaccggt ttggttcaga caacttcagt 360
cttccacctt ccagcctacc aataagacct tcaccatcac ctatggatct gggagcatga 420
agggatttct tgcttatgac acagttcgga ttggggacct tgtaagtact gatcagccgt 480
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tgaactaccc caacatatcc ttctctggag ccatccccat ctttgacaac ctgaagaatc 600
aaggtgccat ttctgagcct gtttttgcct tctacttgag caaaaacaag caggagggca 660
gtgtggtgat gtttggtggg gtggaccacc agtactacaa gggagagctc aactggatac 720
cactgattga agcaggcgaa tggagagtac acatggaccg catctccatg aaaagaacgg 780
ttattgcttg ttctgatggc tgtgaggccc ttgtgcacac tgggacatca catatcgaag 840
gcccaggaag actggtgaat aacatacaca ggctcatccg caccaggcca tttgattcca 900
agcactacgt ttcatgtttt gccaccaata ccctgccctc tattactttc atcatcaacg 960
gcatcaagta cccaatgaca gctcgagcct acatctttaa ggattctaga ggccgctgct 1020
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gggcagtgta actcg 1155

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<211> 379
<212> PRT
<213> bovidae

<400> 42
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Val Gln Ile Pro Leu Arg Gln Val Lys Thr Met Arg Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Lys Asn Phe Leu Lys Glu His Pro Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Met Asn Leu Val Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Phe Cys Thr Met Pro Ala Cys Ser Ala Pro Val Trp Phe
100 105 110

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Arg Gln Leu Gln Ser Ser Thr Phe Gln Pro Thr Asn Lys Thr Phe Thr
        115                 120                 125

Ile Thr Tyr Gly Ser Gly Ser Met Lys Gly Phe Leu Ala Tyr Asp Thr
    130                 135                 140

Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu Ser
145                 150                 155                 160

Val Val Glu Tyr Gly Leu Glu Gly Arg Asn Tyr Asp Gly Ala Leu Gly
                165                 170                 175

Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile Phe Asp
            180                 185                 190

Asn Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe Tyr
        195                 200                 205

Leu Ser Lys Asn Lys Gln Glu Gly Ser Val Val Met Phe Gly Gly Val
    210                 215                 220

Asp His Gln Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Leu Ile Glu
225                 230                 235                 240

Ala Gly Glu Trp Arg Val His Met Asp Arg Ile Ser Met Lys Arg Thr
                245                 250                 255

Val Ile Ala Cys Ser Asp Gly Cys Glu Ala Leu Val His Thr Gly Thr
            260                 265                 270

Ser His Ile Glu Gly Pro Gly Arg Leu Val Asn Asn Ile His Arg Leu
        275                 280                 285

Ile Arg Thr Arg Pro Phe Asp Ser Lys His Tyr Val Ser Cys Phe Ala
    290                 295                 300

Thr Asn Thr Leu Pro Ser Ile Thr Phe Ile Ile Asn Gly Ile Lys Tyr
305                 310                 315                 320

Pro Met Thr Ala Arg Ala Tyr Ile Phe Lys Asp Ser Arg Gly Arg Cys
                325                 330                 335

Tyr Ser Ala Phe Lys Glu Asn Thr Val Arg Thr Ser Arg Glu Thr Trp
            340                 345                 350

Ile Leu Gly Asp Ala Phe Leu Arg Arg Tyr Phe Ser Val Phe Asp Arg
        355                 360                 365

Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
    370                 375
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<210> 43
<211> 1154
<212> DNA
<213> bovidae

<400> 43
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tgaacaattt cctgaaggag catgcttaca gactgtccca gatttctttt catggctcaa 180
atctaactat tcacccgctg agaaacatca gggatttgtt ctacatgggt aacatcacca 240
ttggaacacc ccctcaggaa ttcctggttg tctttgacac aggctcatct gacttgtggg 300
ttccctccga cttttgcacc agtccagcct gttctaaaca ctttaggttc agacatcttc 360
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tggaaggaat tgttgctcat gacacagttc ggattgggga ccttgtaagc actgaccagc 480
cgtttggtct aagcatgaca gaatccgggt ttgagggtat acctttttgat ggcgtcttgg 540
gcttgaacta ccccaacata tccttctctg gagccatccc catctttgac aagctgaaga 600
atcaaggtgc catttctgag cctgtttttg ccttctattt gagcaaagac gagcaggagg 660
gcagtgtggt gatgtttggt ggggtggacc accgctacta caagggagag ctcaaatggg 720
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aaggcccaaa aacactggtt gataacatcc agaagctcat cggtgccact ctacggggtt 900
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gctatagcag ctttcaagag accactgtga gtccatctac agagacctgg atcctgggtg 1080
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cacgggcagt gtaa 1154

<210> 44
<211> 380
<212> PRT
<213> bovidae

<400> 44
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Val
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Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Thr Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu His Ala Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe His Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Arg Asp Leu Phe Tyr Met Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Leu Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Asp Phe Cys Thr Ser Pro Ala Cys Ser Lys His Phe Arg
100 105 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Leu Thr Asn Lys Thr Phe
115 120 125

Ser Ile Glu Tyr Gly Ser Gly Thr Met Glu Gly Ile Val Ala His Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Met Thr Glu Ser Gly Phe Glu Gly Ile Pro Phe Asp Gly Val Leu
165 170 175

Gly Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Glu Gln Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Lys Trp Val Pro Leu Ile
225 230 235 240

Glu Ala Gly Asp Trp Ile Val His Met Asp Cys Ile Ser Met Arg Arg
245 250 255

Lys Val Ile Ala Cys Ser Gly Gly Cys Glu Ala Val Val Asp Thr Gly
260 265 270

Val Ser Met Ile Lys Gly Pro Lys Thr Leu Val Asp Asn Ile Gln Lys
275 280 285

Leu Ile Gly Ala Thr Leu Arg Gly Phe Lys His Tyr Val Ser Cys Ser
290 295 300

Ala Val Asp Thr Leu Pro Ser Ile Thr Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Arg Val Pro Ala Arg Ala Tyr Ile Leu Lys Asp Ser Arg Gly Cys
325 330 335

Cys Tyr Ser Ser Phe Gln Glu Thr Thr Val Ser Pro Ser Thr Glu Thr
340 345 350

Trp Ile Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 45
<211> 1168
<212> DNA
<213> bovidae

<400> 45
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tgaacaattt cttgaaggag catccttaca gactgtccca tatttctttt cgtggctcaa 180
atctaactac tctgccgctg agaaacatca gagatatgct ctacgtgggt aacatcacca 240
ttggaacacc ccctcaagaa ttccaggttg tctttgacac aggttcatct gacttgtggg 300
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gcttgaacta ccccaatcta tcctgctctg ggccattcc catctttgat aagctgaaga 600
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gcagtgtggt gatgtttggt ggggtggacc accgctacta caagggagag ctcaactggg 720
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<210> 46
<211> 380
<212> PRT
<213> bovidae

<400> 46
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Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Arg Lys Thr Leu Ser
20 25 30

Gly Lys Asn Thr Leu Asn Asn Phe Leu Lys Glu His Pro Tyr Arg Leu
35 40 45

Ser His Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr Leu Pro Leu Arg
50 55 60

Asn Ile Arg Asp Met Leu Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Asp Phe Cys Thr Ser Pro Ala Cys Ser Thr His Val Arg
100 105 110

Phe Arg His Phe Gln Ser Ser Thr Phe Arg Pro Thr Thr Lys Thr Phe
115 120 125

Arg Ile Ile Tyr Gly Ser Gly Arg Met Lys Gly Val Val Ala His Asp
130 135 140

Thr Val Arg Ile Gly Asn Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Met Ala Glu Tyr Gly Leu Glu Ser Arg Arg Phe Asp Gly Ile Leu
165 170 175

Gly Leu Asn Tyr Pro Asn Leu Ser Cys Ser Gly Ala Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Gln Gly Ala Ile Ser Asp Pro Ile Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Lys Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Arg Ala Gly Asp Trp Ile Val His Val Asp Arg Ile Thr Met Lys Arg
245 250 255

Glu Val Ile Ala Cys Ser Asp Gly Cys Ala Ala Leu Val Asp Thr Gly
260 265 270

Thr Ser Leu Ile Gln Gly Pro Gly Arg Val Ile Asp Asn Ile His Lys
275 280 285

Leu Ile Gly Ala Thr Pro Arg Gly Ser Lys His Tyr Val Ser Cys Ser
290 295 300

Val Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Ala Pro Ala Tyr Ile Leu Lys Asp Ser Arg Gly Tyr
325 330 335

Cys Tyr Thr Ala Phe Lys Glu Gln Arg Val Arg Arg Ser Thr Glu Ser
340 345 350

Trp Leu Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 47
<211> 1158
<212> DNA
<213> bovidae

<400> 47
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atctaactat tcacccactg agaaacatca tggatatgct ctacgtgggt aacatcacca 240
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cattctgtat aagcctggca gaagttgggt ttgacggtat accttttgat ggtgtcttgg 540
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cacgggcagt gtaactcg 1158

<210> 48
<211> 380
<212> PRT
<213> bovidae

<400> 48
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Val Lys Ile Pro Leu Arg Gln Val Lys Thr Met Arg Lys Thr Leu Ser
            20   25   30

Gly Lys Asn Thr Leu Asn Asn Phe Leu Lys Glu His Thr Tyr Ser Leu
        35   40   45

Ser Gln Ile Ser Ser Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
    50   55   60

Asn Ile Met Asp Met Leu Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65   70   75   80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
                85   90   95

Val Pro Ser Val Phe Cys Gln Ser Leu Ala Cys Ala Thr Lys Val Met
            100   105   110

Phe Ile His Leu His Ser Ser Thr Phe Arg His Thr Gln Lys Val Phe
115 120 125

Asn Ile Lys Tyr Asn Thr Gly Arg Met Lys Gly Leu Leu Val Tyr Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Cys Ile
145 150 155 160

Ser Leu Ala Glu Val Gly Phe Asp Gly Ile Pro Phe Asp Gly Val Leu
165 170 175

Gly Leu Asn Tyr Pro Asn Met Ser Phe Ser Gly Ala Ile Pro Ile Phe
180 185 190

Asp Asn Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Lys Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Gln Ala Gly Gly Trp Thr Val His Val Asp Arg Ile Ser Met Lys Arg
245 250 255

Lys Ile Ile Ala Cys Ser Gly Gly Cys Glu Ala Leu Val Asp Thr Gly
260 265 270

Thr Ala Leu Ile Lys Gly Pro Arg Arg Leu Val Asn Asn Ile Gln Lys
275 280 285

Leu Ile Gly Thr Thr Pro Arg Gly Ser Lys His Tyr Val Ser Cys Ser
290 295 300

Val Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Ala Arg Ala Tyr Ile Leu Lys Asp Ser Glu Ser Asn
325 330 335

Cys Tyr Thr Thr Phe Lys Glu Asn Thr Val Arg Thr Ser Arg Glu Thr
340 345 350

Trp Ile Leu Gly Asp Val Phe Pro Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 49
<211> 1158
<212> DNA
<213> bovidae

<400> 49
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ctgaacaatt tcctgaagga acatgcttac agactgtccc agatttcttc ttgtggctca 180
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aaaggcatca actacccagt gccagctcaa gcctacatcc tcaaggattc tagaggccac 1020
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ggtgacgtct tcctgaggcg gtatttctcg gtctttgatc gaggaaatga caggattggc 1140
ctggcacggg cagtgtaa 1158

<210> 50
<211> 381
<212> PRT
<213> bovidae

<400> 50
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
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Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Arg Lys Thr Leu Ser
20 25 30

Gly Lys Asn Ile Leu Asn Asn Phe Leu Lys Glu His Ala Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Ser Cys Gly Ser Asn Leu Thr Phe His Pro Leu Arg
50 55 60

Asn Ile Lys Asp Arg Leu Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Thr Ser Val Phe Cys Thr Ser Pro Thr Cys Ser Thr His Val Met
100 105 110

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Phe Arg His Phe Asp Ser Ser Thr Phe Arg Pro Thr Lys Lys Thr Phe
        115                 120                 125

Ser Ile Asn Tyr Gly Ser Gly Arg Met Lys Gly Val Val Val His Asp
    130                 135                 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145                 150                 155                 160

Ser Val Val Glu Leu Gly Phe Asp Gly Ile Pro Phe Asp Gly Val Met
                165                 170                 175

Gly Leu Asn Tyr Pro Lys Leu Ser Phe Ser Gly Ala Ile Pro Ile Phe
            180                 185                 190

Asp Asn Leu Arg Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
        195                 200                 205

Tyr Leu Ser Lys Asp Glu Gln Glu Gly Ser Val Val Met Phe Gly Gly
    210                 215                 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Leu Ile
225                 230                 235                 240

Gln Ala Gly Asp Trp Ser Val His Met Asp Ser Ile Ser Met Lys Arg
                245                 250                 255

Lys Val Ile Ala Cys Ser Gly Gly Cys Lys Ala Val Val Asp Thr Gly
            260                 265                 270

Thr Ser Leu Ile Glu Gly Pro Arg Arg Leu Val Asn Asn Ile Gln Lys
        275                 280                 285

Leu Ile Arg Ala Met Pro Arg Gly Ser Glu Tyr Tyr Val Ser Cys Ser
    290                 295                 300

Ala Val Asn Thr Leu Pro Pro Ile Ile Phe Thr Ile Lys Gly Ile Asn
305                 310                 315                 320

Tyr Pro Val Pro Ala Gln Ala Tyr Ile Leu Lys Asp Ser Arg Gly His
                325                 330                 335

Cys Tyr Thr Thr Phe Lys Glu Asp Arg Leu Ser Pro Pro Ser Thr Glu
            340                 345                 350

Thr Trp Ile Leu Gly Asp Val Phe Leu Arg Arg Tyr Phe Ser Val Phe
        355                 360                 365

Asp Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
    370                 375                 380
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<210> 51
<211> 1154
<212> DNA
<213> bovidae

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Gly Leu Asn Tyr Pro Asn Ile Ser Phe Ser Lys Ala Ile Pro Ile Phe
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Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
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Tyr Leu Ser Lys Asp Lys Gln Lys Gly Ser Val Val Met Phe Gly Gly
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            260                 265                 270

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Cys Tyr Thr Thr Phe Lys Glu Lys Arg Val Arg Arg Ser Thr Glu Phe
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Asn Ile Glu Asp Leu Met Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
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Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Phe Trp
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Phe Arg Gln His Gln Ser Ser Thr Phe Arg Pro Thr Asn Lys Thr Phe
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SEQUENCE LISTING

<110> Roberts, R. Michael
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gcaaccgtgc ccaccccaaa cccgcgcgcg cgtgtgcgca cacacacaca cacacacccc 1260
gcagtcaggg cattcctgcc caggggccgg cttgaactgt gtcttcggct ctgccaatcc 1320
cttctcccag tggagaataa aagacctcat cttccacggt 1360

<210> 16
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 16
cccaagctta tgaagtggct tgtgctcct 29

<210> 17
<211> 69
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 17
gggaagctta cttgtcatcg tcgtccttgt agtcggtacc cacctgtgcc aggccaatcc 60
tgtcatttc 69

<210> 18
<211> 21
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 18
cctcttttgc cttctacttg a 21

<210> 19
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 19
gcgctcgagt tacactgccc gtgccaggc 29

<210> 20
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 20
tgggtaacat caccattgga a 21

<210> 21
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 21
tttctgagcc tgtttttgcc 20

<210> 22
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 22
tgggtaacat caccattgga ac 22

<210> 23
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 23
caaacatcac cacactgccc tcc 23

<210> 24
<211> 380
<212> PRT
<213> bovidae

<400> 24
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Leu Lys Thr Met Arg Asn Val Val Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu His Ala Tyr Ser Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr His Pro Leu Arg
50 55 60

Asn Ile Lys Asp Leu Val Tyr Met Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Ala Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Asp Phe Cys Thr Ser Pro Ala Cys Ser Thr His Val Arg
100 105 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Leu Thr Asn Lys Thr Phe
115 120 125

Arg Ile Thr Tyr Gly Ser Gly Arg Met Lys Gly Val Val Val His Asp
130 135 140

Thr Val Arg Ile Gly Asn Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Ile Glu Glu Tyr Gly Phe Glu Gly Arg Ile Tyr Asp Gly Val Leu
165 170 175

Gly Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Gln Arg Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Glu Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Glu Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Gln Ala Gly Asp Trp Ser Val His Met Asp Arg Ile Ser Ile Glu Arg
245 250 255

Lys Ile Ile Ala Cys Ser Asp Gly Cys Lys Ala Leu Val Asp Thr Gly
260 265 270

Thr Ser Asp Ile Val Gly Pro Arg Arg Leu Val Asn Asn Ile His Arg
275 280 285

Leu Ile Gly Ala Ile Pro Arg Gly Ser Glu His Tyr Val Pro Cys Ser
290 295 300

Glu Val Asn Thr Leu Pro Ser Ile Val Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Gly Arg Ala Tyr Ile Leu Lys Asp Asp Arg Gly Arg
325 330 335

Cys Tyr Thr Thr Phe Gln Glu Asn Arg Val Ser Ser Ser Thr Glu Thr
340 345 350

Trp Tyr Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 25
<211> 376

<212> PRT
<213> bovidae

<400> 25

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Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Leu Ser Glu Cys Ile
 1               5                  10                  15

Val Ile Leu Pro Leu Lys Lys Met Lys Thr Leu Arg Glu Thr Leu Arg
            20                  25                  30

Glu Lys Asn Leu Leu Asn Asn Phe Leu Glu Glu Gln Ala Tyr Arg Leu
        35                  40                  45

Ser Lys Asn Asp Ser Lys Ile Thr Ile His Pro Leu Arg Asn Tyr Leu
    50                  55                  60

Asp Thr Ala Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro Pro Gln Glu
 65                  70                  75                  80

Phe Arg Val Val Phe Asp Thr Gly Ser Ala Asn Leu Trp Val Pro Cys
                85                  90                  95

Ile Thr Cys Thr Ser Pro Ala Cys Tyr Thr His Lys Thr Phe Asn Pro
            100                 105                 110

Gln Asn Ser Ser Ser Phe Arg Glu Val Gly Ser Pro Ile Thr Ile Phe
        115                 120                 125

Tyr Gly Ser Gly Ile Ile Gln Gly Phe Leu Gly Ser Asp Thr Val Arg
    130                 135                 140

Ile Gly Asn Leu Val Ser Pro Glu Gln Ser Phe Gly Leu Ser Leu Glu
145                 150                 155                 160

Glu Tyr Gly Phe Asp Ser Leu Pro Phe Asp Gly Ile Leu Gly Leu Ala
                165                 170                 175

Phe Pro Ala Met Gly Ile Glu Asp Thr Ile Pro Ile Phe Asp Asn Leu
            180                 185                 190

Trp Ser His Gly Ala Phe Ser Glu Pro Val Phe Ala Phe Tyr Leu Asn
        195                 200                 205

Thr Asn Lys Pro Glu Gly Ser Val Val Met Phe Gly Gly Val Asp His
    210                 215                 220

Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Val Ser Gln Thr Ser
225                 230                 235                 240
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His Trp Gln Ile Ser Met Asn Asn Ile Ser Met Asn Gly Thr Val Thr
245 250 255

Ala Cys Ser Cys Gly Cys Glu Ala Leu Leu Asp Thr Gly Thr Ser Met
260 265 270

Ile Tyr Gly Pro Thr Lys Leu Val Thr Asn Ile His Lys Leu Met Asn
275 280 285

Ala Arg Leu Glu Asn Ser Glu Tyr Val Val Ser Cys Asp Ala Val Lys
290 295 300

Thr Leu Pro Pro Val Ile Phe Asn Ile Asn Gly Ile Asp Tyr Pro Leu
305 310 315 320

Arg Pro Gln Ala Tyr Ile Ile Lys Ile Gln Asn Ser Cys Arg Ser Val
325 330 335

Phe Gln Gly Gly Thr Glu Asn Ser Ser Leu Asn Thr Trp Ile Leu Gly
340 345 350

Asp Ile Phe Leu Arg Gln Tyr Phe Ser Val Phe Asp Arg Lys Asn Arg
355 360 365

Arg Ile Gly Leu Ala Pro Ala Val
370 375

<210> 26
<211> 381
<212> PRT
<213> bovidae

<400> 26
Met Asp Asp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Arg Asn Thr Val Ser
20 25 30

Gly Lys Asn Ile Leu Asn Asn Ile Leu Lys Glu His Val Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr His Pro Leu Arg
50 55 60

Asn Ile Lys Asp Leu Ile Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro

65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Phe Trp
85 90 95

Val Pro Ser Asp Phe Cys Thr Ser Arg Ala Cys Ser Thr His Val Arg
100 105 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Leu Thr Asn Lys Thr Phe
115 120 125

Arg Ile Thr Tyr Gly Ser Gly Arg Met Lys Gly Val Val Ala His Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Val Glu Glu Tyr Gly Phe Glu Gly Arg Ala Tyr Tyr Asp Gly Val
165 170 175

Leu Gly Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile
180 185 190

Phe Asp Asn Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala
195 200 205

Ile Leu Leu Ser Lys Asp Glu Gln Glu Gly Ser Val Val Met Phe Gly
210 215 220

Gly Val Asp His Arg Tyr Tyr Glu Gly Glu Leu Asn Trp Val Pro Leu
225 230 235 240

Ile Glu Ala Gly Asp Trp Ile Ile His Met Asp Arg Ile Ser Met Lys
245 250 255

Arg Lys Ile Ile Ala Cys Ser Gly Ser Cys Glu Ala Ile Val Asp Thr
260 265 270

Gly Thr Ser Ala Ile Glu Gly Pro Arg Lys Leu Val Asn Lys Ile His
275 280 285

Lys Leu Ile Gly Ala Arg Pro Arg His Ser Lys Tyr Tyr Ile Ser Cys
290 295 300

Ser Ala Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile
305 310 315 320

Asn Tyr Pro Cys Pro Gly Arg Ala Tyr Val Leu Lys Asp Ser Arg Gly

325 330 335

Arg Cys Tyr Ser Met Phe Gln Glu Asn Lys Val Ser Ser Ser Thr Glu
340 345 350

Thr Trp Ile Leu Gly Asp Val Phe Leu Arg Val Tyr Phe Ser Val Phe
355 360 365

Asp Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 27
<211> 380
<212> PRT
<213> bovidae

<400> 27
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Thr Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Val Lys Glu His Ala Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Arg Asp Phe Phe Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Glu Leu Trp
85 90 95

Val Pro Ser Ile Phe Cys Asn Ser Ser Thr Cys Ser Lys His Asp Arg
100 105 110

Phe Arg His Leu Glu Ser Ser Thr Phe Arg Leu Ser Arg Arg Thr Phe
115 120 125

Ser Ile Thr Tyr Gly Ser Gly Arg Ile Glu Ala Leu Val Val His Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Gln Phe Gly Leu
145 150 155 160

Cys Leu Glu Glu Ser Gly Phe Glu Gly Met Arg Phe Asp Gly Val Leu
165 170 175

Gly Leu Ser Tyr Thr Asn Ile Ser Pro Ser Gly Ala Ile Pro Ile Phe
180 185 190

Tyr Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Glu Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Ala Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Leu Met
225 230 235 240

Lys Ala Gly Asp Trp Ser Val His Met Asp Arg Ile Ser Met Lys Arg
245 250 255

Lys Val Ile Ala Cys Ser Gly Gly Cys Lys Ala Leu Val Asp Thr Gly
260 265 270

Ser Ser Asp Ile Val Gly Pro Ser Thr Leu Val Asn Asn Ile Trp Lys
275 280 285

Leu Ile Gly Ala Thr Pro Gln Gly Ser Glu His Tyr Val Ser Cys Ser
290 295 300

Ala Val Asn Ser Leu Pro Ser Ile Ile Phe Thr Ile Lys Ser Asn Asn
305 310 315 320

Tyr Arg Val Pro Gly Gln Ala Tyr Ile Leu Lys Asp Ser Arg Gly Arg
325 330 335

Cys Phe Thr Ala Phe Lys Gly His Gln Gln Ser Ser Ser Thr Glu Met
340 345 350

Trp Ile Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Arg Lys Asp Arg Ile Gly Leu Ala Thr Lys Val
370 375 380

<210> 28
<211> 377
<212> PRT
<213> bovidae

<400> 28

Met Lys Trp Leu Val Leu Leu Gly Leu Leu Thr Ser Ser Glu Cys Ile
1   5   10   15

Val Ile Leu Pro Leu Thr Lys Val Lys Thr Met Arg Lys Thr Leu Ser
            20   25   30

Glu Lys Asn Met Leu Asn Asn Phe Leu Lys Glu Gln Ala Tyr Arg Leu
        35   40   45

Ser Gln Ile Ser Ser Arg Gly Ser Asn Ile Thr Ile His Pro Leu Arg
    50   55   60

Asn Ile Met Asp Met Val Tyr Val Gly Lys Ile Thr Ile Gly Thr Pro
65   70   75   80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Glu Leu Trp
                85   90   95

Val Pro Ser Val Phe Cys Pro Ser Ser Ala Cys Ser Thr His Ile Arg
            100   105   110

Phe Arg His Leu Glu Ser Ser Thr Ser Gly Leu Thr Gln Lys Thr Phe
        115   120   125

Ser Ile Thr Tyr Gly Ser Gly Ser Thr Lys Gly Phe Leu Ala Tyr Asp
    130   135   140

Thr Val Arg Ile Gly Asp Leu Leu Ser Thr Asp Gln Glu Phe Gly Leu
145   150   155   160

Ser Met Glu Glu His Gly Phe Glu Asp Leu Pro Phe Asp Gly Val Leu
                165   170   175

Gly Leu Asn Tyr Pro Asp Met Ser Phe Ile Thr Thr Ile Pro Ile Phe
            180   185   190

Asp Asn Leu Lys Asn Gln Gly Ala Phe Ser Glu Pro Val Phe Ala Phe
        195   200   205

Tyr Leu Gly Lys Val Lys Gly Ser Val Val Met Phe Gly Gly Val Asp
    210   215   220

His Thr Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile Gln Ala
225   230   235   240

Gly Glu Trp Ser Leu His Met Asp Arg Ile Ser Met Lys Arg Lys Val
                245   250   255

Ile Ala Cys Ser Gly Gly Cys Glu Ala Phe Tyr Asp Thr Gly Thr Ser
260 265 270

Leu Ile Leu Gly Pro Arg Arg Leu Val Asn Asn Ile Gln Lys Leu Ile
275 280 285

Gly Ala Thr Pro Gln Gly Ser Glu His Tyr Ile Ser Cys Phe Ala Val
290 295 300

Ile Ser Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn Ile Pro
305 310 315 320

Val Pro Ala Arg Ala Tyr Ile His Lys Asp Ser Arg Gly His Cys Tyr
325 330 335

Pro Thr Phe Lys Glu Asn Thr Val Ser Thr Ser Thr Glu Thr Trp Ile
340 345 350

Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp Arg Gly
355 360 365

Asn Asp Arg Ile Gly Leu Ala Gln Val
370 375

<210> 29
<211> 379
<212> PRT
<213> bovidae

<400> 29
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Arg Asn Ala Ile Ser
20 25 30

Gly Lys Asn Thr Leu Asn Asn Ile Leu Lys Glu His Ala Tyr Arg Leu
35 40 45

Pro Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr His Pro Leu Arg Asn
50 55 60

Ile Arg Asp Leu Phe Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro Pro
65 70 75 80

Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Asp Leu Trp Val

85 90 95

Ala Ser Ile Phe Cys Asn Ser Ser Ser Cys Ala Ala His Val Arg Phe
100 105 110

Arg His His Gln Ser Ser Thr Phe Arg Pro Thr Asn Lys Thr Phe Arg
115 120 125

Ile Thr Tyr Gly Ser Gly Arg Met Lys Gly Val Val Val His Asp Thr
130 135 140

Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu Cys
145 150 155 160

Leu Lys Asp Ser Gly Phe Lys Gly Ile Pro Phe Asp Gly Ile Leu Gly
165 170 175

Leu Ser Tyr Pro Asn Lys Thr Phe Ser Gly Ala Phe Pro Ile Phe Asp
180 185 190

Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe Tyr
195 200 205

Leu Ser Lys Asp Lys Gln Glu Gly Ser Val Val Met Phe Gly Gly Val
210 215 220

Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile Gln
225 230 235 240

Val Gly Asp Trp Phe Val His Met Asp Arg Thr Thr Met Lys Arg Lys
245 250 255

Val Ile Ala Cys Ser Asp Gly Cys Lys Ala Leu Val Asp Thr Gly Thr
260 265 270

Ser Asp Ile Val Gly Pro Ser Thr Leu Val Asn Asn Ile Trp Lys Leu
275 280 285

Ile Arg Ala Arg Pro Leu Gly Pro Gln Tyr Phe Val Ser Cys Ser Ala
290 295 300

Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn Tyr
305 310 315 320

Arg Leu Pro Ala Arg Ala Tyr Ile His Lys Asp Ser Arg Gly Arg Cys
325 330 335

Tyr Thr Ala Phe Lys Glu His Arg Phe Ser Ser Pro Ile Glu Thr Trp

340 345 350

Leu Leu Gly Asp Val Phe Leu Arg Arg Tyr Phe Ser Val Phe Asp Arg
355 360 365

Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375

<210> 30
<211> 341
<212> PRT
<213> bovidae

<400> 30
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Arg Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu Asp Pro Tyr Arg Leu
35 40 45

Ser His Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Arg Asp Ile Phe Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Ile Asp Cys Asn Ser Thr Ser Cys Ala Thr His Val Arg
100 105 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Pro Thr Asn Lys Thr Phe
115 120 125

Arg Ile Ile Tyr Gly Ser Gly Arg Met Asn Gly Val Ile Ala Tyr Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Val Glu Glu Tyr Gly Phe Ala His Lys Arg Phe Asp Gly Ile Leu
165 170 175

Gly Leu Asn Tyr Trp Asn Leu Ser Trp Ser Lys Ala Met Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Asn Ile Thr Met Asn Arg Glu Val Ile Ala Cys Ser Glu
210 215 220

Gly Cys Ala Ala Leu Val Asp Thr Gly Ser Ser Asn Ile Gln Gly Pro
225 230 235 240

Gly Arg Leu Ile Asp Asn Ile Gln Arg Ile Ile Gly Ala Thr Pro Arg
245 250 255

Gly Ser Lys Tyr Tyr Val Ser Cys Ser Ala Val Asn Ile Leu Pro Ser
260 265 270

Ile Ile Phe Thr Ile Asn Gly Val Asn Tyr Pro Val Pro Pro Arg Ala
275 280 285

Tyr Ile Leu Lys Asp Ser Arg Gly His Cys Tyr Thr Thr Phe Lys Glu
290 295 300

Lys Arg Val Arg Arg Ser Thr Glu Ser Trp Val Leu Gly Glu Val Phe
305 310 315 320

Leu Arg Leu Tyr Phe Ser Val Phe Asp Arg Gly Asn Asp Arg Ile Gly
325 330 335

Leu Ala Arg Arg Val
340

<210> 31
<211> 387
<212> PRT
<213> bovidae

<400> 31
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Leu Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Thr Lys Met Lys Thr Met Gln Glu Ala Ile Arg
20 25 30

Glu Lys Gln Leu Leu Glu Asp Phe Leu Asp Glu Gln Pro His Ser Leu
35 40 45

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Ser Gln His Ser Asp Pro Asp Lys Lys Phe Ser Ser His Gln Leu Lys
    50                  55                  60

Asn Phe Gln Asn Ala Val Tyr Phe Gly Thr Ile Thr Ile Gly Thr Pro
65                  70                  75                  80

Pro Gln Glu Phe Gln Val Asn Phe Asp Thr Gly Ser Ser Asp Leu Trp
                85                  90                  95

Val Pro Ser Val Asp Cys Gln Ser Pro Ser Cys Ser Lys His Lys Arg
            100                 105                 110

Phe Asp Pro Gln Lys Ser Thr Thr Phe Gln Pro Leu Asn Gln Lys Ile
        115                 120                 125

Glu Leu Val Tyr Gly Ser Gly Thr Met Lys Gly Val Leu Gly Ser Asp
    130                 135                 140

Thr Ile Gln Ile Gly Asn Leu Val Ile Val Asn Gln Ile Phe Gly Leu
145                 150                 155                 160

Ser Gln Asn Gln Ser Ser Gly Val Leu Glu Gln Val Pro Tyr Asp Gly
                165                 170                 175

Ile Leu Gly Leu Ala Tyr Pro Ser Leu Ala Ile Gln Gly Thr Thr Pro
            180                 185                 190

Val Phe Asp Asn Leu Lys Asn Arg Glu Val Ile Ser Glu Pro Val Phe
        195                 200                 205

Ala Phe Tyr Leu Ser Ser Arg Pro Glu Asn Ile Ser Thr Val Met Phe
    210                 215                 220

Gly Gly Val Asp His Thr Tyr His Lys Gly Lys Leu Gln Trp Ile Pro
225                 230                 235                 240

Val Thr Gln Ala Arg Phe Trp Gln Val Ala Met Ser Ser Met Thr Met
                245                 250                 255

Asn Gly Asn Val Val Gly Cys Ser Gln Gly Cys Gln Ala Val Val Asp
            260                 265                 270

Thr Gly Thr Ser Leu Leu Val Gly Pro Thr His Leu Val Thr Asp Ile
        275                 280                 285

Leu Lys Leu Ile Asn Pro Asn Pro Ile Leu Asn Asp Glu Gln Met Leu
    290                 295                 300
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Ser Cys Asp Ala Ile Asn Ser Leu Pro Thr Leu Leu Leu Thr Ile Asn
305 310 315 320

Gly Ile Val Tyr Pro Val Pro Pro Asp Tyr Tyr Ile Gln Arg Phe Ser
325 330 335

Glu Arg Ile Cys Phe Ile Ser Phe Gln Gly Gly Thr Glu Ile Leu Lys
340 345 350

Asn Leu Gly Thr Ser Glu Thr Trp Ile Leu Gly Asp Val Phe Leu Arg
355 360 365

Leu Tyr Phe Ser Val Tyr Asp Arg Gly Asn Asn Arg Ile Gly Leu Ala
370 375 380

Pro Ala Ala
385

<210> 32
<211> 379
<212> PRT
<213> bovidae

<400> 32
Met Lys Trp Ile Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Gln Val Lys Thr Met Arg Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Lys Asn Phe Leu Lys Glu His Pro Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Met Asn Leu Val Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Phe Cys Thr Met Pro Ala Cys Ser Ala Pro Val Trp Phe
100 105 110

Arg Gln Leu Gln Ser Ser Thr Phe Gln Pro Thr Asn Lys Thr Phe Thr

115 120 125

Ile Thr Tyr Gly Ser Gly Ser Met Lys Gly Phe Leu Ala Tyr Asp Thr
130 135 140

Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu Ser
145 150 155 160

Val Val Glu Tyr Gly Leu Glu Gly Arg Asn Tyr Asp Gly Val Leu Gly
165 170 175

Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile Phe Asp
180 185 190

Asn Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe Tyr
195 200 205

Leu Ser Lys Asn Lys Gln Glu Gly Ser Val Val Met Phe Gly Gly Val
210 215 220

Asp His Gln Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Leu Ile Glu
225 230 235 240

Ala Gly Glu Trp Arg Val His Met Asp Arg Ile Ser Met Lys Arg Thr
245 250 255

Val Ile Ala Cys Ser Asp Gly Cys Glu Ala Leu Val His Thr Gly Thr
260 265 270

Ser His Ile Glu Gly Pro Gly Arg Leu Val Asn Asn Ile His Arg Leu
275 280 285

Ile Arg Thr Arg Pro Phe Asp Ser Lys His Tyr Val Ser Cys Phe Ala
290 295 300

Thr Lys Tyr Leu Pro Ser Ile Thr Phe Ile Ile Asn Gly Ile Lys Tyr
305 310 315 320

Pro Met Thr Ala Arg Ala Tyr Ile Phe Lys Asp Ser Arg Gly Arg Cys
325 330 335

Tyr Ser Ala Phe Lys Glu Asn Thr Val Arg Thr Ser Arg Glu Thr Trp
340 345 350

Ile Leu Gly Asp Ala Phe Leu Arg Arg Tyr Phe Ser Val Phe Asp Arg
355 360 365

Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val

370 375

<210> 33
<211> 380
<212> PRT
<213> bovidae

<400> 33
Met Lys Trp Leu Gly Leu Leu Gly Leu Val Ala Leu Ser Glu Cys Met
1 5 10 15

Val Ile Ile Pro Leu Arg Gln Met Lys Thr Met Arg Glu Thr Leu Arg
20 25 30

Glu Arg His Leu Leu Thr Asn Phe Ser Glu Glu His Pro Tyr Asn Leu
35 40 45

Ser Gln Lys Ala Ala Asn Asp Gln Asn Ile Ile Tyr His His Pro Leu
50 55 60

Arg Ser Tyr Lys Asp Phe Ser Tyr Ile Gly Asn Ile Asn Ile Gly Thr
65 70 75 80

Pro Pro Gln Glu Phe Gln Val Leu Phe Asp Thr Gly Ser Ser Ser Leu
85 90 95

Trp Val Pro Ser Ile Tyr Cys Gln Ser Ser Ser Cys Tyr Lys His Asn
100 105 110

Ser Phe Val Pro Cys Asn Ser Ser Thr Phe Lys Ala Thr Asn Lys Ile
115 120 125

Phe Asn Thr Asn Tyr Thr Ala Thr Ser Ile Lys Gly Tyr Leu Val Tyr
130 135 140

Asp Thr Val Arg Ile Gly Asn Leu Val Ser Val Ala Gln Pro Phe Gly
145 150 155 160

Leu Ser Leu Lys Glu Phe Gly Phe Asp Asp Val Pro Phe Asp Gly Ile
165 170 175

Leu Gly Leu Gly Tyr Pro Arg Arg Thr Ile Thr Gly Ala Asn Pro Ile
180 185 190

Phe Asp Asn Leu Trp Lys Gln Gly Val Ile Ser Glu Pro Val Phe Ala
195 200 205

Phe Tyr Leu Ser Ser Gln Lys Glu Asn Gly Ser Val Val Met Phe Gly
    210   215   220

Gly Val Asn Arg Ala Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Val
225   230   235   240

Ser Gln Val Gly Ser Trp His Ile Asn Ile Asp Ser Ile Ser Met Asn
                245   250   255

Gly Thr Val Val Ala Cys Lys Arg Gly Cys Gln Ala Ser Trp Ile Arg
            260   265   270

Gly Arg Leu Ser Ala Trp Pro Lys Arg Ile Val Ser Lys Ile Gln Lys
        275   280   285

Leu Ile His Ala Arg Pro Ile Asp Arg Glu His Val Val Ser Cys Gln
    290   295   300

Ala Ile Gly Thr Leu Pro Pro Ala Val Phe Thr Ile Asn Gly Ile Asp
305   310   315   320

Tyr Pro Val Pro Ala Gln Ala Tyr Ile Gln Ser Leu Ser Gly Tyr Cys
                325   330   335

Phe Ser Asn Phe Leu Val Arg Pro Gln Arg Val Asn Glu Ser Glu Thr
            340   345   350

Trp Ile Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
        355   360   365

Arg Gly Asn Asn Arg Ile Gly Leu Ala Pro Ala Val
    370   375   380

<210> 34
<211> 376
<212> PRT
<213> bovidae

<400> 34
Met Lys Trp Leu Val Phe Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
  1   5   10   15

Val Ile Met Leu Leu Thr Lys Thr Lys Thr Met Arg Glu Ile Trp Arg
            20   25   30

Glu Lys Lys Leu Leu Asn Ser Phe Leu Glu Glu Gln Ala Asn Arg Met
        35   40   45

Ser Asp Asp Ser Ala Ser Asp Pro Lys Leu Ser Thr His Pro Leu Arg
50 55 60

Asn Ala Leu Asp Met Ala Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Lys Glu Phe Arg Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Ile Lys Cys Ile Ser Pro Ala Cys His Thr His Ile Thr
100 105 110

Phe Asp His His Lys Ser Ser Thr Phe Arg Leu Thr Arg Arg Pro Phe
115 120 125

His Ile Leu Tyr Gly Ser Gly Met Met Asn Gly Val Leu Ala Tyr Asp
130 135 140

Thr Val Arg Ile Gly Lys Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Leu Gln Gln Phe Gly Phe Asp Asn Ala Pro Phe Asp Gly Val Leu
165 170 175

Gly Leu Ser Tyr Pro Ser Leu Ala Val Pro Gly Thr Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Gln Gln Gly Ala Ile Ser Glu Pro Ile Phe Ala Phe
195 200 205

Tyr Leu Ser Thr Arg Lys Glu Asn Gly Ser Val Leu Met Leu Gly Gly
210 215 220

Val Asp His Ser Tyr His Lys Gly Lys Leu Asn Trp Ile Pro Val Ser
225 230 235 240

Gln Thr Lys Ser Trp Leu Ile Thr Val Asp Arg Ile Ser Met Asn Gly
245 250 255

Arg Val Ile Gly Cys Glu His Gly Cys Glu Ala Leu Val Asp Thr Gly
260 265 270

Thr Ser Leu Ile His Gly Pro Ala Arg Pro Val Thr Asn Ile Gln Lys
275 280 285

Phe Ile His Ala Met Pro Tyr Gly Ser Glu Tyr Met Val Leu Cys Pro
290 295 300

Val Ile Ser Ile Leu Pro Pro Val Ile Phe Thr Ile Asn Gly Ile Asp
305 310 315 320

Tyr Ser Val Pro Arg Glu Ala Tyr Ile Gln Lys Ile Ser Asn Ser Leu
325 330 335

Cys Leu Ser Thr Phe His Gly Asp Asp Thr Asp Gln Trp Ile Leu Gly
340 345 350

Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Tyr Asp Arg Gly Asn Asn
355 360 365

Arg Ile Gly Leu Ala Pro Ala Val
370 375

<210> 35
<211> 375
<212> PRT
<213> bovidae

<400> 35
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1 5 10 15

Val Ile Leu Pro Leu Arg Lys Met Lys Thr Leu Arg Glu Thr Leu Arg
20 25 30

Glu Lys Asn Leu Leu Asn Asn Phe Leu Glu Glu Arg Ala Tyr Arg Leu
35 40 45

Ser Lys Lys Asp Ser Lys Ile Thr Ile His Pro Leu Lys Asn Tyr Leu
50 55 60

Asp Met Ala Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro Pro Gln Glu
65 70 75 80

Phe Arg Val Val Phe Asp Thr Gly Ser Ala Asp Leu Trp Val Pro Ser
85 90 95

Ile Ser Cys Val Ser Pro Ala Cys Tyr Thr His Lys Thr Phe Asn Leu
100 105 110

His Asn Ser Ser Ser Phe Gly Gln Thr His Gln Pro Ile Ser Ile Ser
115 120 125

Tyr Gly Pro Gly Ile Ile Gln Gly Phe Leu Gly Ser Asp Thr Val Arg

130 135 140

Ile Gly Asn Leu Val Ser Leu Lys Gln Ser Phe Gly Leu Ser Gln Glu
145 150 155 160

Glu Tyr Gly Phe Asp Gly Ala Pro Phe Asp Gly Val Leu Gly Leu Ala
165 170 175

Tyr Pro Ser Ile Ser Ile Lys Gly Ile Ile Pro Ile Phe Asp Asn Leu
180 185 190

Trp Ser Gln Gly Ala Phe Ser Glu Pro Val Phe Ala Phe Tyr Leu Asn
195 200 205

Thr Cys Gln Pro Glu Gly Ser Val Val Met Phe Gly Gly Val Asp His
210 215 220

Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Val Ser Gln Thr Arg
225 230 235 240

Tyr Trp Gln Ile Ser Met Asn Arg Ile Ser Met Asn Gly Asn Val Thr
245 250 255

Ala Cys Ser Arg Gly Cys Gln Ala Leu Leu Asp Thr Gly Thr Ser Met
260 265 270

Ile His Gly Pro Thr Arg Leu Ile Thr Asn Ile His Lys Leu Met Asn
275 280 285

Ala Arg His Gln Gly Ser Glu Tyr Val Val Ser Cys Asp Ala Val Lys
290 295 300

Thr Leu Pro Pro Val Ile Phe Asn Ile Asn Gly Ile Asp Tyr Pro Leu
305 310 315 320

Pro Pro Gln Ala Tyr Ile Thr Lys Ala Gln Asn Phe Cys Leu Ser Ile
325 330 335

Phe His Gly Gly Thr Glu Thr Ser Ser Pro Glu Thr Trp Ile Leu Gly
340 345 350

Gly Val Phe Leu Arg Gln Tyr Phe Ser Val Phe Asp Arg Arg Asn Asp
355 360 365

Ser Ile Gly Leu Ala Gln Val
370 375

<210> 36
<211> 391
<212> PRT
<213> bovidae

<400> 36
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Val Ile Leu Pro Leu Lys Lys Met Lys Thr Leu Arg Glu Thr Leu Arg
20 25 30

Glu Lys Asn Leu Leu Asn Asn Phe Leu Glu Glu Gln Ala Tyr Arg Leu
35 40 45

Ser Lys Asn Asp Ser Lys Ile Thr Ile His Pro Leu Arg Asn Tyr Leu
50 55 60

Asp Thr Ala Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro Pro Gln Glu
65 70 75 80

Phe Arg Val Val Phe Asp Thr Gly Ser Ala Asn Leu Trp Val Pro Cys
85 90 95

Ile Thr Cys Thr Ser Pro Ala Cys Tyr Thr His Lys Thr Phe Asn Pro
100 105 110

Gln Asn Ser Ser Ser Phe Arg Glu Val Gly Ser Pro Ile Thr Ile Phe
115 120 125

Tyr Gly Ser Gly Ile Ile Gln Gly Phe Leu Gly Ser Asp Thr Val Arg
130 135 140

Ile Gly Asn Leu Val Ser Leu Lys Gln Ser Phe Gly Leu Ser Gln Glu
145 150 155 160

Glu Tyr Gly Phe Asp Gly Ala Pro Phe Asp Gly Val Leu Gly Leu Ala
165 170 175

Tyr Pro Ser Ile Ser Ile Lys Gly Ile Ile Pro Ile Phe Asp Asn Leu
180 185 190

Trp Ser His Gly Ala Phe Ser Glu Pro Val Phe Ala Phe Tyr Leu Asn
195 200 205

Thr Asn Lys Pro Glu Gly Ser Val Val Met Phe Gly Gly Val Asp His
210 215 220

Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Val Ser Gln Thr Ser
225 230 235 240

His Trp Gln Ile Ser Met Asn Asn Ile Ser Met Asn Gly Thr Val Thr
245 250 255

Ala Cys Ser Cys Gly Cys Glu Ala Leu Leu Asp Thr Gly Thr Ser Met
260 265 270

Ile Tyr Gly Pro Thr Lys Leu Val Thr Asn Ile His Lys Leu Met Asn
275 280 285

Ala Arg Leu Glu Asn Ser Glu Tyr Val Val Ser Cys Asp Ala Val Lys
290 295 300

Thr Leu Pro Pro Val Ile Phe Asn Ile Asn Gly Ile Asp Tyr Pro Leu
305 310 315 320

Arg Pro Gln Ala Tyr Ile Ile Lys Ile Gln Asn Asn Cys Arg Ser Val
325 330 335

Phe Gln Gly Gly Thr Glu Asn Ser Ser Leu Asn Thr Trp Ile Leu Gly
340 345 350

Asp Ile Phe Leu Arg Gln Tyr Phe Ser Val Phe Asp Arg Lys Asn Arg
355 360 365

Arg Ile Cys Trp His Arg Trp Val Pro Thr Thr Arg Thr Thr Met Thr
370 375 380

Ser Lys Leu Pro Pro Lys Leu
385 390

<210> 37
<211> 392
<212> PRT
<213> bovidae

<400> 37
Met Lys Trp Leu Val Leu Leu Ala Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Ile Lys Ile Pro Leu Arg Arg Val Lys Thr Met Ser Asn Thr Ala Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Lys His Pro Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr His Pro Leu Met
50 55 60

Asn Ile Trp Asp Leu Leu Tyr Leu Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Leu Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Leu Leu Cys Asn Ser Ser Thr Cys Ala Lys His Val Met
100 105 110

Phe Arg His Arg Leu Ser Ser Thr Tyr Arg Pro Thr Asn Lys Thr Phe
115 120 125

Met Ile Phe Tyr Ala Val Gly Lys Ile Glu Gly Val Val Val Arg Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Ala Asp Gln Thr Phe Gly Leu
145 150 155 160

Ser Ile Ala Glu Thr Gly Phe Glu Asn Thr Thr Leu Asp Gly Ile Leu
165 170 175

Gly Leu Ser Tyr Pro Asn Thr Ser Cys Phe Gly Thr Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Leu His Ser
195 200 205

Val Arg Arg Lys Asp Glu Gln Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Ser Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Lys Ala Gly Asp Trp Ser Val Arg Val Asp Ser Ile Thr Met Lys Arg
245 250 255

Glu Val Ile Ala Cys Ser Asp Gly Cys Arg Ala Leu Val Asp Thr Gly
260 265 270

Ser Ser His Ile Gln Gly Pro Gly Arg Leu Ile Asp Asn Val Gln Lys
275 280 285

Leu Ile Gly Thr Met Pro Gln Gly Ser Met His Tyr Val Pro Cys Ser
290 295 300

Ala Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Ser Ile Ser
305   310   315   320

Tyr Thr Val Pro Ala Gln Ala Tyr Ile Leu Lys Gly Ser Arg Gly Arg
                325   330   335

Cys Tyr Ser Thr Phe Gln Gly His Thr Met Ser Ser Ser Thr Glu Thr
            340   345   350

Trp Ile Leu Gly Asp Val Phe Leu Ser Gln Tyr Phe Ser Val Phe Asp
        355   360   365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Gln Val Gly Thr Asp Tyr Lys
    370   375   380

Asp Asp Asp Glu Ser Pro Lys Leu
385   390

<210> 38
<211> 388
<212> PRT
<213> Felis domestica

<400> 38
Met Lys Trp Leu Trp Val Leu Gly Leu Val Ala Leu Ser Glu Cys Leu
1   5   10   15

Val Thr Ile Pro Leu Thr Arg Val Lys Ser Met Arg Glu Asn Leu Arg
            20   25   30

Glu Lys Asp Arg Leu Lys Asp Phe Leu Glu Asn His Pro Tyr Asn Leu
        35   40   45

Ala Tyr Lys Phe Val Asp Ser Val Asn Leu Asp Leu Gly Ile Tyr Phe
    50   55   60

Glu Pro Met Arg Asn Tyr Leu Asp Leu Ala Tyr Val Gly Thr Ile Ser
65   70   75   80

Ile Gly Thr Pro Pro Gln Glu Phe Lys Val Ile Phe Asp Thr Gly Ser
                85   90   95

Ser Asp Leu Trp Val Pro Ser Ile Tyr Cys Ser Ser Pro Ala Cys Ala
            100   105   110

Asn His Asn Val Phe Asn Pro Leu Arg Ser Ser Thr Phe Arg Ile Ser

115 120 125

Gly Arg Pro Ile His Leu Gln Tyr Gly Ser Gly Thr Met Ser Gly Phe
130 135 140

Leu Ala Tyr Asp Thr Val Arg Phe Gly Gly Leu Val Asp Val Ala Gln
145 150 155 160

Ala Phe Gly Leu Ser Leu Arg Glu Pro Gly Lys Phe Met Glu Tyr Ala
165 170 175

Val Phe Asp Gly Ile Leu Gly Leu Ala Tyr Pro Ser Leu Ser Leu Arg
180 185 190

Gly Thr Val Pro Val Phe Asp Asn Leu Trp Lys Gln Gly Leu Ile Ser
195 200 205

Gln Glu Leu Phe Ala Phe Tyr Leu Ser Lys Lys Asp Glu Glu Gly Ser
210 215 220

Val Val Met Phe Gly Gly Val Asp His Ser Tyr Tyr Ser Gly Asp Leu
225 230 235 240

Asn Trp Val Pro Val Ser Lys Arg Leu Tyr Trp Gln Leu Ser Met Asp
245 250 255

Ser Ile Ser Met Asn Gly Glu Val Ile Ala Cys Asp Gly Gly Cys Gln
260 265 270

Ala Ile Ile Asp Thr Gly Thr Ser Leu Leu Ile Gly Pro Ser His Val
275 280 285

Val Phe Asn Ile Gln Met Ile Ile Gly Ala Asn Gln Ser Tyr Ser Gly
290 295 300

Glu Tyr Val Val Asp Cys Asp Ala Ala Asn Thr Leu Pro Asp Ile Val
305 310 315 320

Phe Thr Ile Asn Gly Ile Asp Tyr Pro Val Pro Ala Ser Ala Tyr Ile
325 330 335

Gln Glu Gly Pro Gln Gly Thr Cys Tyr Ser Gly Phe Asp Glu Ser Gly
340 345 350

Asp Ser Leu Leu Val Ser Asp Ser Trp Ile Leu Gly Asp Val Phe Leu
355 360 365

Arg Leu Tyr Phe Thr Val Phe Asp Arg Glu Asn Asn Arg Ile Gly Leu

370 375 380

Ala Leu Ala Val
385

<210> 39
<211> 1158
<212> DNA
<213> bovidae

<400> 39
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tgaacaattt cttgaaggag gatccttaca gactgtccca gatttctttt cgtggctcaa 180
atctaactat tcacccgctg agaaacatca gagatatctt ctatgtcgga aacatcacca 240
ttggaacacc ccctcaggaa ttccaggtta tctttgacac aggctcatct gacttgtggg 300
tgccctcgat cgattgcaac agtacatcct gtgctacaca tgttaggttc agacatcttc 360
agtcttccac cttccggcct accaataaga ccttcaggat catctatgga tctgggagaa 420
tgaacggagt tattgcttat gacacagttc ggattgggga ccttgtaagt accgaccagc 480
catttggtct aagcgtggag gaatatgggt ttgcgcacaa aagatttgat ggcatcttgg 540
gcttgaacta ctggaaccta tcctggtcta aggccatgcc catctttgac aagctgaaga 600
atgaaggcgc catttctgag cctgtttttg ccttctactt gagcaaagac aagcgggagg 660
gcagtgtggt gatgtttggt ggggtggacc accgctacta caagggagag ctcaagtggg 720
taccactgat ccaagcagtc gactggagtg tacacgtaga ccgcatcacc atgaacagag 780
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ccaagtacta cgtttcatgt tctgcggtca atatcctgcc ctctattatc ttcaccatca 960
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gctataccac ctttaaagag aaaagagtga ggagatctac agagagctgg gtcctgggtg 1080
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cacgggcagt gtaactcg 1158

<210> 40
<211> 380
<212> PRT
<213> bovidae

<400> 40
Met Lys Trp Leu Val Val Leu Gly Leu Val Ala Phe Ser Glu Cys Ile
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Arg Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu Asp Pro Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Arg Asp Ile Phe Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Ile Asp Cys Asn Ser Thr Ser Cys Ala Thr His Val Arg
100 105 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Pro Thr Asn Lys Thr Phe
115 120 125

Arg Ile Ile Tyr Gly Ser Gly Arg Met Asn Gly Val Ile Ala Tyr Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Val Glu Glu Tyr Gly Phe Ala His Lys Arg Phe Asp Gly Ile Leu
165 170 175

Gly Leu Asn Tyr Trp Asn Leu Ser Trp Ser Lys Ala Met Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Lys Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Lys Trp Val Pro Leu Ile
225 230 235 240

Gln Ala Val Asp Trp Ser Val His Val Asp Arg Ile Thr Met Asn Arg
245 250 255

Glu Val Ile Ala Cys Ser Glu Gly Cys Ala Ala Leu Val Asp Thr Gly
260 265 270

Ser Ser Asn Ile Gln Gly Pro Arg Arg Leu Ile Asp Asn Ile Gln Arg
275 280 285

Ile Ile Gly Ala Thr Pro Arg Gly Ser Lys Tyr Tyr Val Ser Cys Ser
290 295 300

Ala Val Asn Ile Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Val Asn
305   310   315   320

Tyr Pro Val Pro Pro Arg Ala Tyr Ile Leu Lys Asp Ser Arg Gly His
                325   330   335

Cys Tyr Thr Thr Phe Lys Glu Lys Arg Val Arg Arg Ser Thr Glu Ser
            340   345   350

Trp Val Leu Gly Glu Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
        355   360   365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
    370   375   380

<210> 41
<211> 1155
<212> DNA
<213> bovidae

<400> 41
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tgaagaattt cttgaaggag catccttaca gactgtccca gatttctttt cgtggctcaa 180
atctaactat tcacccgctg aggaacatca tgaatttggt ctacgtgggt aacatcacca 240
ttggaacacc ccctcaggaa ttccaggttg tctttgacac aggctcatct gacttgtggg 300
tgccctcctt ttgtaccatg ccagcatgct ctgcaccggt ttggttcaga caacttcagt 360
cttccacctt ccagcctacc aataagacct tcaccatcac ctatggatct gggagcatga 420
agggatttct tgcttatgac acagttcgga ttggggacct tgtaagtact gatcagccgt 480
tcggtctaag cgtggtggaa tatgggttgg agggcagaaa ttatgatggt gccttgggct 540
tgaactaccc caacatatcc ttctctggag ccatccccat ctttgacaac ctgaagaatc 600
aaggtgccat ttctgagcct gtttttgcct tctacttgag caaaaacaag caggagggca 660
gtgtggtgat gtttggtggg gtggaccacc agtactacaa gggagagctc aactggatac 720
cactgattga agcaggcgaa tggagagtac acatggaccg catctccatg aaaagaacgg 780
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gggcagtgta actcg 1155

<210> 42
<211> 379
<212> PRT
<213> bovidae

<400> 42

Met Lys Trp Ile Val Leu Leu Gly Leu Met Ala Phe Ser Glu Cys Ile
1   5   10   15

Val Gln Ile Pro Leu Arg Gln Val Lys Thr Met Arg Lys Thr Leu Ser
            20   25   30

Gly Lys Asn Met Leu Lys Asn Phe Leu Lys Glu His Pro Tyr Arg Leu
        35   40   45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
    50   55   60

Asn Ile Met Asn Leu Val Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65   70   75   80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
                85   90   95

Val Pro Ser Phe Cys Thr Met Pro Ala Cys Ser Ala Pro Val Trp Phe
            100   105   110

Arg Gln Leu Gln Ser Ser Thr Phe Gln Pro Thr Asn Lys Thr Phe Thr
        115   120   125

Ile Thr Tyr Gly Ser Gly Ser Met Lys Gly Phe Leu Ala Tyr Asp Thr
    130   135   140

Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu Ser
145   150   155   160

Val Val Glu Tyr Gly Leu Glu Gly Arg Asn Tyr Asp Gly Ala Leu Gly
                165   170   175

Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile Phe Asp
            180   185   190

Asn Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe Tyr
        195   200   205

Leu Ser Lys Asn Lys Gln Glu Gly Ser Val Val Met Phe Gly Gly Val
    210   215   220

Asp His Gln Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Leu Ile Glu
225   230   235   240

Ala Gly Glu Trp Arg Val His Met Asp Arg Ile Ser Met Lys Arg Thr
                245   250   255

Val Ile Ala Cys Ser Asp Gly Cys Glu Ala Leu Val His Thr Gly Thr
260 265 270

Ser His Ile Glu Gly Pro Gly Arg Leu Val Asn Asn Ile His Arg Leu
275 280 285

Ile Arg Thr Arg Pro Phe Asp Ser Lys His Tyr Val Ser Cys Phe Ala
290 295 300

Thr Asn Thr Leu Pro Ser Ile Thr Phe Ile Ile Asn Gly Ile Lys Tyr
305 310 315 320

Pro Met Thr Ala Arg Ala Tyr Ile Phe Lys Asp Ser Arg Gly Arg Cys
325 330 335

Tyr Ser Ala Phe Lys Glu Asn Thr Val Arg Thr Ser Arg Glu Thr Trp
340 345 350

Ile Leu Gly Asp Ala Phe Leu Arg Arg Tyr Phe Ser Val Phe Asp Arg
355 360 365

Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375

<210> 43
<211> 1154
<212> DNA
<213> bovidae

<400> 43
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tgaacaattt cctgaaggag catgcttaca gactgtccca gatttctttt catggctcaa 180
atctaactat tcacccgctg agaaacatca gggatttgtt ctacatgggt aacatcacca 240
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agtcttccac attccggctt accaataaga ccttcagcat tgaatacgga tctgggacaa 420
tggaaggaat tgttgctcat gacacagttc ggattgggga ccttgtaagc actgaccagc 480
cgtttggtct aagcatgaca gaatccgggt ttgagggtat acctttttgat ggcgtcttgg 540
gcttgaacta ccccaacata tccttctctg gagccatccc catctttgac aagctgaaga 600
atcaaggtgc catttctgag cctgtttttg ccttctattt gagcaaagac gagcaggagg 660
gcagtgtggt gatgtttggt ggggtggacc accgctacta caagggagag ctcaaatggg 720
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tcaagcacta cgtttcatgt tctgcagtcg ataccctgcc ctctattacc ttcaccataa 960

acggtatcaa ctaccgagtg ccagctcgag cctacatcct caaggattct agaggctgct 1020
gctatagcag ctttcaagag accactgtga gtccatctac agagacctgg atcctgggtg 1080
acgtcttcct gagactgtat ttctcagtct ttgatcgagg aaatgacagg attgggctgg 1140
cacgggcagt gtaa 1154

<210> 44
<211> 380
<212> PRT
<213> bovidae

<400> 44
Met Lys Trp Leu Val Leu Leu Gly Leu Val Ala Phe Ser Glu Cys Val
1 5 10 15

Val Lys Ile Pro Leu Arg Arg Val Lys Thr Met Thr Lys Thr Leu Ser
20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu His Ala Tyr Arg Leu
35 40 45

Ser Gln Ile Ser Phe His Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Arg Asp Leu Phe Tyr Met Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Leu Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Asp Phe Cys Thr Ser Pro Ala Cys Ser Lys His Phe Arg
100 105 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Leu Thr Asn Lys Thr Phe
115 120 125

Ser Ile Glu Tyr Gly Ser Gly Thr Met Glu Gly Ile Val Ala His Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Met Thr Glu Ser Gly Phe Glu Gly Ile Pro Phe Asp Gly Val Leu
165 170 175

Gly Leu Asn Tyr Pro Asn Ile Ser Phe Ser Gly Ala Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe

195 200 205

Tyr Leu Ser Lys Asp Glu Gln Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Lys Trp Val Pro Leu Ile
225 230 235 240

Glu Ala Gly Asp Trp Ile Val His Met Asp Cys Ile Ser Met Arg Arg
245 250 255

Lys Val Ile Ala Cys Ser Gly Gly Cys Glu Ala Val Val Asp Thr Gly
260 265 270

Val Ser Met Ile Lys Gly Pro Lys Thr Leu Val Asp Asn Ile Gln Lys
275 280 285

Leu Ile Gly Ala Thr Leu Arg Gly Phe Lys His Tyr Val Ser Cys Ser
290 295 300

Ala Val Asp Thr Leu Pro Ser Ile Thr Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Arg Val Pro Ala Arg Ala Tyr Ile Leu Lys Asp Ser Arg Gly Cys
325 330 335

Cys Tyr Ser Ser Phe Gln Glu Thr Thr Val Ser Pro Ser Thr Glu Thr
340 345 350

Trp Ile Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 45
<211> 1168
<212> DNA
<213> bovidae

<400> 45
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tgaacaattt cttgaaggag catccttaca gactgtccca tatttctttt cgtggctcaa 180
atctaactac tctgccgctg agaaacatca gagatatgct ctacgtgggt aacatcacca 240
ttggaacacc ccctcaagaa ttccaggttg tctttgacac aggttcatct gacttgtggg 300
tgccctctga cttttgcacc agtccagcct gttctacaca cgttaggttc agacattttc 360

agtcttccac cttccggcct accactaaga ccttcaggat catctatgga tctgggagaa 420
tgaaaggagt tgttgcgcat gacacagttc ggattgggaa ccttgtaagt actgaccagc 480
cgttcggcct aagcatggcg gaatacgggt tggagagcag aagatttgat ggcatcttgg 540
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<210> 46
<211> 380
<212> PRT
<213> bovidae

<400> 46
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Gly Lys Asn Thr Leu Asn Asn Phe Leu Lys Glu His Pro Tyr Arg Leu
        35   40   45

Ser His Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr Leu Pro Leu Arg
    50   55   60

Asn Ile Arg Asp Met Leu Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65   70   75   80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
                85   90   95

Val Pro Ser Asp Phe Cys Thr Ser Pro Ala Cys Ser Thr His Val Arg
            100   105   110

Phe Arg His Phe Gln Ser Ser Thr Phe Arg Pro Thr Thr Lys Thr Phe
        115   120   125

Arg Ile Ile Tyr Gly Ser Gly Arg Met Lys Gly Val Val Ala His Asp
    130   135   140

Thr Val Arg Ile Gly Asn Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145   150   155   160

Ser Met Ala Glu Tyr Gly Leu Glu Ser Arg Arg Phe Asp Gly Ile Leu
                165   170   175

Gly Leu Asn Tyr Pro Asn Leu Ser Cys Ser Gly Ala Ile Pro Ile Phe
            180   185   190

Asp Lys Leu Lys Asn Gln Gly Ala Ile Ser Asp Pro Ile Phe Ala Phe
        195   200   205

Tyr Leu Ser Lys Asp Lys Arg Glu Gly Ser Val Val Met Phe Gly Gly
    210   215   220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile
225   230   235   240

Arg Ala Gly Asp Trp Ile Val His Val Asp Arg Ile Thr Met Lys Arg
                245   250   255

Glu Val Ile Ala Cys Ser Asp Gly Cys Ala Ala Leu Val Asp Thr Gly
            260   265   270

Thr Ser Leu Ile Gln Gly Pro Gly Arg Val Ile Asp Asn Ile His Lys
        275   280   285

Leu Ile Gly Ala Thr Pro Arg Gly Ser Lys His Tyr Val Ser Cys Ser
    290   295   300

Val Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn
305   310   315   320

Tyr Pro Val Pro Ala Pro Ala Tyr Ile Leu Lys Asp Ser Arg Gly Tyr
                325   330   335

Cys Tyr Thr Ala Phe Lys Glu Gln Arg Val Arg Arg Ser Thr Glu Ser
            340   345   350

Trp Leu Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
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Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
    370   375   380

<210> 47
<211> 1158

<212> DNA
<213> bovidae

<400> 47
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tgaacaattt cttgaaggaa catacttaca gtctgtccca gatttcttct cgtggttcaa 180
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cacgggcagt gtaactcg 1158

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<211> 380
<212> PRT
<213> bovidae

<400> 48
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35 40 45

Ser Gln Ile Ser Ser Arg Gly Ser Asn Leu Thr Ile His Pro Leu Arg
50 55 60

Asn Ile Met Asp Met Leu Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Val Phe Cys Gln Ser Leu Ala Cys Ala Thr Lys Val Met
100 105 110

Phe Ile His Leu His Ser Ser Thr Phe Arg His Thr Gln Lys Val Phe
115 120 125

Asn Ile Lys Tyr Asn Thr Gly Arg Met Lys Gly Leu Leu Val Tyr Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Cys Ile
145 150 155 160

Ser Leu Ala Glu Val Gly Phe Asp Gly Ile Pro Phe Asp Gly Val Leu
165 170 175

Gly Leu Asn Tyr Pro Asn Met Ser Phe Ser Gly Ala Ile Pro Ile Phe
180 185 190

Asp Asn Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Lys Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Gln Ala Gly Gly Trp Thr Val His Val Asp Arg Ile Ser Met Lys Arg
245 250 255

Lys Ile Ile Ala Cys Ser Gly Gly Cys Glu Ala Leu Val Asp Thr Gly
260 265 270

Thr Ala Leu Ile Lys Gly Pro Arg Arg Leu Val Asn Asn Ile Gln Lys
275 280 285

Leu Ile Gly Thr Thr Pro Arg Gly Ser Lys His Tyr Val Ser Cys Ser
290 295 300

Val Val Asn Thr Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Ala Arg Ala Tyr Ile Leu Lys Asp Ser Glu Ser Asn
325 330 335

Cys Tyr Thr Thr Phe Lys Glu Asn Thr Val Arg Thr Ser Arg Glu Thr
340 345 350

Trp Ile Leu Gly Asp Val Phe Pro Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 49
<211> 1158
<212> DNA
<213> bovidae

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aatctaactt ttcacccctt gagaaacatc aaggataggc tctacgtggg taacatcacc 240
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aaggttattg cttgctctgg tggctgcaag gccgttgtgg acaccgggac atcactgatt 840
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<211> 381
<212> PRT
<213> bovidae

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20 25 30

Gly Lys Asn Ile Leu Asn Asn Phe Leu Lys Glu His Ala Tyr Arg Leu

35 40 45

Ser Gln Ile Ser Ser Cys Gly Ser Asn Leu Thr Phe His Pro Leu Arg
50 55 60

Asn Ile Lys Asp Arg Leu Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Ile Phe Asp Thr Gly Ser Ser Asp Leu Trp
85 90 95

Val Thr Ser Val Phe Cys Thr Ser Pro Thr Cys Ser Thr His Val Met
100 105 110

Phe Arg His Phe Asp Ser Ser Thr Phe Arg Pro Thr Lys Lys Thr Phe
115 120 125

Ser Ile Asn Tyr Gly Ser Gly Arg Met Lys Gly Val Val Val His Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Val Val Glu Leu Gly Phe Asp Gly Ile Pro Phe Asp Gly Val Met
165 170 175

Gly Leu Asn Tyr Pro Lys Leu Ser Phe Ser Gly Ala Ile Pro Ile Phe
180 185 190

Asp Asn Leu Arg Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Glu Gln Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Ile Pro Leu Ile
225 230 235 240

Gln Ala Gly Asp Trp Ser Val His Met Asp Ser Ile Ser Met Lys Arg
245 250 255

Lys Val Ile Ala Cys Ser Gly Gly Cys Lys Ala Val Val Asp Thr Gly
260 265 270

Thr Ser Leu Ile Glu Gly Pro Arg Arg Leu Val Asn Asn Ile Gln Lys
275 280 285

Leu Ile Arg Ala Met Pro Arg Gly Ser Glu Tyr Tyr Val Ser Cys Ser

290 295 300

Ala Val Asn Thr Leu Pro Pro Ile Ile Phe Thr Ile Lys Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Ala Gln Ala Tyr Ile Leu Lys Asp Ser Arg Gly His
325 330 335

Cys Tyr Thr Thr Phe Lys Glu Asp Arg Leu Ser Pro Pro Ser Thr Glu
340 345 350

Thr Trp Ile Leu Gly Asp Val Phe Leu Arg Arg Tyr Phe Ser Val Phe
355 360 365

Asp Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

<210> 51
<211> 1154
<212> DNA
<213> bovidae

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<210> 52
<211> 380
<212> PRT

<213> bovidae

<400> 52

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            20                  25                  30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu His Ala Tyr Arg Leu
        35                  40                  45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Ser His Pro Leu Arg
    50                  55                  60

Asn Ile Lys Asp Leu Val Tyr Leu Ala Asn Ile Thr Ile Gly Thr Pro
65                  70                  75                  80

Pro Gln Glu Phe Gln Val Phe Leu Asp Thr Gly Ser Ser Asp Leu Trp
                85                  90                  95

Val Pro Ser Asp Phe Cys Thr Ser Pro Gly Cys Ser Lys His Val Arg
            100                 105                 110

Phe Arg His Leu Gln Ser Ser Thr Phe Arg Leu Thr Asn Lys Thr Phe
        115                 120                 125

Ser Ile Thr Tyr Gly Ser Gly Arg Ile Lys Gly Val Val Ala His Asp
    130                 135                 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Ser Leu
145                 150                 155                 160

Ser Met Ala Glu Tyr Gly Leu Glu His Ile Pro Phe Asp Gly Ile Leu
                165                 170                 175

Gly Leu Asn Tyr Pro Asn Val Ser Ser Ser Gly Ala Ile Pro Ile Phe
            180                 185                 190

Asp Lys Leu Lys Asn Gln Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
        195                 200                 205

Tyr Leu Ser Lys Asp Lys Gln Glu Gly Ser Val Val Met Phe Gly Gly
    210                 215                 220

Val Asp His Arg Tyr Tyr Arg Gly Lys Leu Asn Trp Val Pro Leu Ile
225                 230                 235                 240
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Gln Ala Gly Asn Trp Ile Ile His Met Asp Ser Ile Ser Ile Glu Arg
245 250 255

Lys Val Ile Ala Cys Ser Gly Gly Cys Val Ala Phe Val Asp Ile Gly
260 265 270

Thr Ala Phe Ile Glu Gly Pro Lys Pro Leu Val Asp Asn Met Gln Lys
275 280 285

Leu Ile Arg Ala Lys Pro Trp Arg Ser Lys His Tyr Val Ser Cys Ser
290 295 300

Ala Val Asn Thr Leu Pro Ser Ile Thr Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Gly Arg Ala Tyr Ile Leu Lys Asp Ser Arg Arg Arg
325 330 335

Cys Tyr Ser Thr Phe Lys Glu Ile Pro Leu Ser Pro Thr Thr Glu Phe
340 345 350

Trp Met Leu Gly Asp Val Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

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<211> 1154
<212> DNA
<213> bovidae

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<211> 380
<212> PRT
<213> bovidae

<400> 54
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20 25 30

Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu His Pro Tyr Lys Leu
35 40 45

Ser Gln Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr Leu Pro Leu Arg
50 55 60

Asn Ile Trp Asp Ile Phe Tyr Ile Gly Thr Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Ala Ser Ser Asp Leu Trp
85 90 95

Val Pro Ser Ile Ile Cys Asn Ser Ser Thr Cys Ser Thr His Val Arg
100 105 110

Phe Arg His Arg Gln Ser Ser Thr Phe Arg Leu Thr Asn Lys Thr Phe
115 120 125

Gly Ile Thr Tyr Gly Ser Gly Arg Met Lys Gly Val Val Val His Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Val Ala Glu Tyr Gly Phe Glu Gly Arg Arg Phe Asp Gly Val Leu
165 170 175

Gly Leu Asn Tyr Pro Asn Ile Ser Phe Ser Lys Ala Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Val Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Asp Lys Gln Lys Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Arg Ala Gly Asp Trp Ser Val His Val Asp Arg Ile Thr Met Lys Gly
245 250 255

Glu Val Ile Gly Cys Ser Asp Gly Cys Thr Ala Met Val Asp Thr Gly
260 265 270

Ser Ser Asn Ile Gln Gly Pro Gly Arg Val Ile Asp Asn Ile His Lys
275 280 285

Leu Ile Gly Ala Thr Pro Arg Gly Ser Lys His Tyr Val Ser Cys Ser
290 295 300

Ala Val Ser Ala Leu Pro Ser Val Val Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Ala Arg Ala Tyr Val Leu Lys Asp Phe Thr Gly Asn
325 330 335

Cys Tyr Thr Thr Phe Lys Glu Lys Arg Val Arg Arg Ser Thr Glu Phe
340 345 350

Trp Ile Leu Gly Glu Ala Phe Leu Arg Leu Tyr Phe Ser Val Phe Asp
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Arg Gly Asn Asp Arg Ile Gly Leu Ala Arg Ala Val
370 375 380

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<211> 1320
<212> DNA
<213> bovidae

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catgctgaac aatttcttga aggagcatgg taacagattg tccaagattt cttttcgtgg 180
ctcaaatcta actactctcc cgctgagaaa catcgaggat ttgatgtacg tgggtaacat 240

caccattgga acaccccac aggaattcca ggttgtcttt gatacaggct catctgactt 300
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acatcagtct tccaccttcc ggcctaccaa taagaccttc agcatcacct atggatctgg 420
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<210> 56
<211> 380
<212> PRT
<213> bovidae

<400> 56
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Gly Lys Asn Met Leu Asn Asn Phe Leu Lys Glu His Gly Asn Arg Leu
35 40 45

Ser Lys Ile Ser Phe Arg Gly Ser Asn Leu Thr Thr Leu Pro Leu Arg
50 55 60

Asn Ile Glu Asp Leu Met Tyr Val Gly Asn Ile Thr Ile Gly Thr Pro
65 70 75 80

Pro Gln Glu Phe Gln Val Val Phe Asp Thr Gly Ser Ser Asp Phe Trp
85 90 95

Val Pro Ser Asp Phe Cys Thr Ser Pro Asp Cys Ile Thr His Val Arg
100 105 110

Phe Arg Gln His Gln Ser Ser Thr Phe Arg Pro Thr Asn Lys Thr Phe
115 120 125

Ser Ile Thr Tyr Gly Ser Gly Arg Met Arg Gly Val Val Val His Asp
130 135 140

Thr Val Arg Ile Gly Asp Leu Val Ser Thr Asp Gln Pro Phe Gly Leu
145 150 155 160

Ser Val Ser Glu Tyr Gly Phe Lys Asp Arg Ala Tyr Asp Gly Ile Leu
165 170 175

Gly Leu Asn Tyr Pro Asp Glu Ser Phe Ser Glu Ala Ile Pro Ile Phe
180 185 190

Asp Lys Leu Lys Asn Glu Gly Ala Ile Ser Glu Pro Ile Phe Ala Phe
195 200 205

Tyr Leu Ser Lys Lys Lys Arg Glu Gly Ser Val Val Met Phe Gly Gly
210 215 220

Val Asp His Arg Tyr Tyr Lys Gly Glu Leu Asn Trp Val Pro Leu Ile
225 230 235 240

Glu Glu Gly Asp Trp Ser Val Arg Met Asp Gly Ile Ser Met Lys Thr
245 250 255

Lys Val Val Ala Cys Ser Asp Gly Cys Glu Ala Val Val Asp Thr Gly
260 265 270

Thr Ser Leu Ile Lys Gly Pro Arg Lys Leu Val Asn Lys Ile Gln Lys
275 280 285

Leu Ile Gly Ala Thr Pro Arg Gly Ser Lys His Tyr Val Tyr Cys Ser
290 295 300

Ala Val Asn Ala Leu Pro Ser Ile Ile Phe Thr Ile Asn Gly Ile Asn
305 310 315 320

Tyr Pro Val Pro Ala Arg Ala Tyr Ile Leu Lys Asp Ser Arg Gly Arg
325 330 335

Cys Tyr Thr Ala Phe Lys Lys Gln Arg Phe Ser Ser Ser Thr Glu Thr
340 345 350

Trp Leu Leu Gly Asp Ala Phe Leu Arg Val Tyr Phe Ser Val Phe Asp
355 360 365

Arg Gly Asn Gly Arg Ile Gly Leu Ala Gln Ala Val
370 375 380